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(54) Title: POLYPEPTIDES OF G-COUPLED RECEPTOR PROTEINS, AND COMPOSITIONS AND METHODS THEREOF

(57) Abstract

Compounds, compositions and methods involving purified, isolated and/or synthetic G-protein coupled receptor (GPR) polypeptides that comprise fragments, derivatives and/or consensus peptides of transmembrane domains of G-coupled receptor proteins, wherein the GPR polypeptide has biological activity selected from binding of a GPR ligand to a GPR or modulating the binding of GPR a ligand to a GPR.

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POLYPEPTIDES OF G-COUPLED RECEPTOR PROTEINS, AND COMPOSITIONS AND METHODS THEREOF

FIELD OF THE INVENTION

The present invention relates to compounds, compositions and methods involving synthetic, isolated and/or recombinant G-protein coupled receptor polypeptides that comprise fragments and/or consensus peptides of G-protein coupled receptors.

BACKGROUND OF THE INVENTION

The membrane protein gene superfamily of G-protein coupled receptors (GPRs) has been characterized as having seven putative transmembrane domains. The domains are believed to represent transmembrane α -helices connected by extracellular or cytoplasmic loops. Of the 74 sequenced members of this G-protein receptor superfamily, the shortest sequence of 324 amino acids represents the rat mas oncogene and the longest, of 744 amino acids, represents the human thyroid-stimulating hormone (TSH) receptor. GPRs thus include a wide range of biologically active receptors, such as hormone-, viral-, growth factor- and neuroreceptors.

G-protein coupled receptors have been characterized as including these seven conserved hydrophobic stretches of about 20-30 amino acids, connecting at least 8 divergent hydrophilic loops. The G-protein family of coupled receptors includes dopamine receptors which bind in a noncovalent but high affinity manner to neuroleptic drugs used for treating psychotic and neurological disorders. For example, the dopamine D_2 receptor includes these transmembrane domains, two of which (TM III and TM V; see below) have been implicated by site-selective mutagenesis to demonstrate functional, association with D_2

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TM6 and TM7 are the most highly conserved and are postulated to

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provide sequences which impart biological activity to GPRs. Most GPRs have single conserved cysteine residues in each of the first two extracellular loops which form disulfide bonds that are believed to stabilize functional protein structure. TM3 is also implicated in signal transduction.

Phosphorylation and lipidation (palmitylation or farnesylation) of cysteine residues can influence signal transduction of some GPRs. Most GPRs contain potential phosphorylation sites (e.g., serine or theronine residues) within the third cytoplasmic loop and/or the carboxy terminus. For several GPRs, such as the β -adrenoreceptor, phosphorylation by protein kinase A and/or specific receptor kinases mediates receptor desensitization.

Non-limiting examples of GPRs include cAMP receptors, adenosine receptors, β -adrenergic receptors, muscarinic acetylcholine receptors, α -adrenergic receptors, serotonin receptors (5-HT), histamine H2 receptors, thrombin receptors, kinin receptors, follicle stimulating hormone receptors, opsins and rhodopsins, odorant receptors, cytomegalovirus receptor, etc. See e.g., Probst et al DNA and Cell Biology 11:1-20(1992), which is entirely incorporated herein by reference.

The ligand binding sites of GPRs are believed to comprise a hydrophilic socket formed by several GPR transmembrane domains, which socket is surrounded by hydrophobic residues of the GPRs. The hydrophilic side of each GPR transmembrane helix is postulated to face inward and form the polar ligand binding site. TM3 has been implicated in several GPRs as having a ligand binding site, such as including the TM3 aspartate residue. Additionally, TM5 serines, a TM6 asparagine and TM6 or TM7 phenylalanines or tyrosines are also implicated in ligand binding.

GPRs can be intracellularly coupled by heterotrimeric G-proteins to various intracellular enzymes, ion channels and transporters. See, e.g., Johnson et al Endoc. Rev. 10:317-331(1989); and Birnbaumer et al Biochem. Biophys. Acta 1031:163-224(1990) which references are incorporated entirely herein by reference. GPR agonist binding catalyzes the exchange

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of GTP for GDP on the α -subunit of the G-protein. Different G-protein α -subunits preferentially stimulate particular effectors to modulate various biological functions in a cell. Phosphorylation of cytoplasmic residues of GPRs has been identified as an important mechanism for the regulation of G-protein coupling of some GPRs.

As a non-limiting example of a GPR ligand, dopamine (3,4-dihydroxyphenethylamine) is a critical neurotransmitter in the central nervous system (e.g., in the substantia nigra, midbrain, and hypothalamus). Since the elucidation of the ascending mesolimbic and nigrostriatal pathways, these pathways have been found to be critical in the control of both motor initiation (nigrostriatal) behavior and affective (mesolimbic) behavior. The clinical efficacy of the major neuroleptic antipsychotic medications has been found to correlate with the respective affinities of these agents for the dopamine D2 receptor in the brain. A dopaminergic role in the symptomatology of the major psychoses has thus been hypothesized, although it is unclear if dopamine alone is etiological, (see, e.g., Davis et al. Am. J. Psych. 148:1474-1476 (1991)). Nonetheless, this hypothesis has served as a stimulus for current research in this area.

One model for studying possible interactions of G-protein coupled receptors with their ligands has emerged from site-directed mutagenesis and biochemical analysis of the β -adrenergic receptor, as well as from biophysical analysis of the interaction of retinal with opsin.

According to such a model, the binding of a GPR ligand to a G-protein coupled receptor involves multiple interactions between functional groups on the GPR ligand and residues within the hydrophophilic binding site of the receptor.

While a number of the amino acid residues in the dopamine D_2 receptor have been postulated to participate in D_2 ligand binding, based on results obtained from site-directed

specifically determine which residues are actually involved in

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binding in the D_2 system. Sibley et al. Soc. Neurosci. Abs. 17:36.10, 324.5, 324.6 (1991).

The clinical use of neuroleptics has provided a means for treating patients suffering from psychotic disorders. Short-term use of neuroleptics is indicated in several types of psychotic disorders, e.g., acute psychotic episodes, regardless of type; exacerbations of schizophrenia; acute manic excitement while deferring use of lithium or awaiting onset of its effects; adjunctive therapy for major depression with prominent psychotic symptoms, or when an antidepressant or ECT alone is not successful; for agitation in delirium, dementia, or severe mental retardation while seeking to identify and treat the primary basis of the problem; in certain chronic, degenerative, or idiopathic neuropsychiatric disorders with dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome; or for ballism or hemiballism; childhood psychoses or apparently allied conditions marked by severe agitation or aggressive behavior; miscellaneous medical indications, notably nausea and vomiting, or intractable hiccups.

Additionally, continuous long-term use of neuroleptics is indicated in many psychotic disorders, such as (for more than six months) (i) primary indications such as Schizophrenia, Paranoia b, Childhood psychoses, some degenerative or idiopathic neuropsychiatric disorders (notably, Huntington's disease and Gilles de la Tourette's syndrome); (ii) secondary indications such as extremely unstable manic-depressive or other episodic psychoses (unusual), otherwise unmanageable behavior symptoms in dementia, amentia, or other brain syndromes; and (iii) questionable indications such as chronic characterological disorders with schizoid, "borderline," or neurotic characteristics; substance abuse; or antisocial behavior, recurrent mood disorders. See, e.g., Baldessarini, Chemotherapy in Psychiatry, Revised and Enlarged Edition, Harvard University Press, Cambridge, MA, (1985), the contents of which is entirely incorporated herein by reference.

Neuroleptics are also referred to as heuroplegics, psychoplegics, psycholeptics, antipsychotics and major

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tranquilizers, but are sometimes distinguished from nonneuroleptic anti-psychotics. Neuroleptics have recently been characterized as an agent that produces sedative or tranquilizing effects, and which also produces motor side effects, such as catalepsy or extrapyramidal symptomatology. Nonlimiting representative examples of neuroleptics include phenothiazine derivatives (e.g., chlorpromazine); thioxanthine derivatives (e.g., thiothixene); butyrophenone derivatives (e.g., haloperidol); dihydroindolone (e.g., molindone); dibenzoxazepine derivatives (e.g., loxapine); and "atypical" neuroleptics (e.g., sulpiride, remoxipiride pimozide and clozapine). See Berstein Clinical Pharmacology Littleton, Mass.: PSG Publishing (1978); Usdin et al Clinical Pharmacology in Psychiatry New York: Elsevier North-Holland (1981); and Baldessarini, supra, (1985); and , which references are herein entirely incorporated by reference.

The term "atypical neuroleptics" has been used to describe antipsychotic neuroleptics that produce few or no extrapyramidal side effects and which do not cause catalepsy in animals (See, e.g., Picket et al, Arch. Gen. Psychiatry 49:345 (May 1992). Alternatively, atypical neuroleptics, such as clozapine, have been described as those neuroleptics which have a higher affinity for D_4 and D_1 sites than for D_2 sites (See, e.g., Davis et al Amer. J. Psych. 148:1474, 1476 (November 1991).

The long term use of all known anti-psychotics, such as neuroleptics or non-neuroleptic antipsychotics, has resulted in serious side effects, as present in Table I, such as persistent and poorly reversible motoric dysfunctions (e.g., tardive dyskinesia) in a significant number of patients. These side effects are especially prevalent in geriatric populations, and adequate pharmacological treatment of these debilitating motoric dysfunctions is not currently available. This problem

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TABLE I Neurological Side Effects of Neuroleptic-Antipsychotic Drugs

Reaction	Features	Period of maximum ris	Proposed mechanism	Treatment
Acute dystonia	Spasm of muscles of tongue, face, neck, back; may mimic seizures; not hysterical	1-5 days	Dopamine excess? Acetylcholine excess?	Antiparkinsonism agents are diagnostic and curative (i.m. or i.v., then p.o.)
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask- facies, shuffling gait	5-30 days (rarely persists)	Dopamine blockade	Antiparkinsonism agents (p.o); dopamine agonists risky?
Akathisia	Motor restlessness; patient may experience anxiety or agitation	5-60 days (commonly persists)	Unknown	Reduce dose or change drug low doses of propranolol;* antiparkinsonism agents or or benzodiazepines may help
Tardive dyskinesia	Oral-facial dyskinesia; choreo-athetosis, some- times irreversible, rarely progressive	6-24 months (worse on withdrawal)	Dopamine excess?	Prevention best; treatment unsatisfactory; slow spontaneous remission
"Rabbit" syndrome	Perioral tremor (late parkinsonism variant?); usually reversible	Months or years	Unknown	Antiparkinsonism agents; reduce dose of neuroleptic
Malignant syndrome	Catatonia, stupor, fever, unstable pulse and blood pressure; myoglobinemia; can be fatal	Weeks	Unknown	Stop neuroleptic; antiparkinsonism agents usually fail; bromocriptine often helps; dantrolene variable; general supportive care crucial

a. There may be an increased risk of hypotension on interacting high doses of propranolol with some antipsychotic agents; clonidine may also be effective at doses of 0.2-0.8 mg/day, but carries a high risk of hypotension (Zubenko et al., *Psychiatry Res.* 11:143, 1984).

In addition, clozapine, although apparently capable of producing less motor side effects, can cause irreversible, potentially fatal agranulocytosis in a minority of patients administered the drug. Such serious side effects limit the use of

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clozapine to patients who are resistant to treatment with other neuroleptics.

Antipsychotics have a variety of significant pharmacological effects, e.g., as presented in the following Tables II and III.

Table II
Comparative Pharmacology of Neuroleptics

	Phenothiazine Derivative	Thioxanthene Derivative	Butyrophenone Derivative	
Alkaloid Pharmacologic Actions	Chlorpromazine	Thiothixene	Haloperidol	
Antipsychotic	Yes + +	Yes + +	Yes + + + +	
Antiemetic	Yes + + +	Not tested	Yes + + +	
Hypothermia	Yes +	Yes +	No	
Hypotension	Yes + +	Yes + + +	+	
Parkinsonism	Yes + +	Yes +	Yes + + + +	
Antiadrenergic	Yes + +	Yes + + +	+	
Anticholinergic	Yes +	Yes +	Negligible	
Antihistaminic	Yes +	Negligible	Negligible	
Releases NE. DA	No	No	No	
Blocks DA	Yes + +	Yes +	Yes + + + +	
Blocks NE	Yes + +	Yes + + +	Yes +	
Central sympathetic suppressant	Yes + +	Yes +	Yes + + +	

Table III

Comparative Pharmacology of Antipsychotics

Extrapyramidal Drug	Sedation	Adrenergic Blockage	Reaction
Chlorpromazine	High	Moderate to high	Moderate
Chlorprothixene	High	High	Low to moderate
Haloperidol	Low	Low	High
Molindone	Moderate	Moderate	Moderate to high
Loxapine	High	Low to moderate	High

See Ebadi, PHARMACOLOGY, Little, Brown and Co., Boston, 61-65 (1985); Cattabeni et al Adv. Biochem. Psychopharmacology 24:275 (1980). Baldessarini, supra, which references are herein incorporated entirely by reference.

However, despite the fact that thousands of neurolepticor antipsychotic-type compounds have been synthesized and reported

discrosed.

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Alternative to dopamine receptor GPRs, as presented above, other neuroreceptor GPRs are involved in neurological pathologies, and drugs such as neuroreceptor GPR binding agents, presently used for treating these pathologies, also suffer from 5 similar side effects as those of neuroleptics, as presented above.

Other GPRs are also involved in receptor-related pathologies, such as hormone related GPRs involved in endocrine related pathologies.

Accordingly, there is a need to provide G-protein coupled 10 receptor binding agents, including neuroreceptor and endocrine receptor GPRs, which do not produce such deleterious and debilitating side effects as those produced by known agents, such as neuroleptics, which can be used for therapy or diagnosis of GPR related pathologies.

Citation of documents herein is not intended as an admission that any of the documents cited herein is pertinent prior art, or an admission that the cited documents are considered material to the patentabilty of the claims of the present application. All statements as to the date or representations as 20 to the contents of these documents are based on the information available to the applicant and does not constitute any admission as to the correctness of the dates or contents of these documents.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to 25 overcome one or more deficiencies found in the related art.

It is another object of the present invention to provide non-naturally occurring synthetic, isolated and/or recombinant GPR polypeptides which are fragments, consensus fragments and/or sequences having conservative amino acid substitutions, of at 30 least one transmembrane domain of at least one G-protein coupled receptor, which polypeptides have been discovered to have receptor-like functional binding sites of neuroreceptor and endocrine GPRs, such that GPR polypeptides of the present invention may bind GPR ligands, or which may also modulate, 35 quantitatively or qualitatively, GPR ligand binding to GPRs.

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It is still another object of the present invention to provide GPR polypeptides and compositions that have only partially helical structures, in contrast to known characterized transmembrane domains of GPRs, such as, but not limited to, GPR transmembrane domains I-VII.

It is yet another object of the present invention to provide synthetic or recombinant GPR polypeptides, conservative substitution derivatives thereof, antibodies, anti-idiotype antibodies, compositions and methods that can be used as potential modulators of G-protein coupled receptor function, by binding to GPR ligands or modulate GPR ligand binding, due to their expected biological properties, which may be used in diagnostic, therapeutic and/or research applications.

It is a further object of the present invention is to
15 provide synthetic, isolated or recombinant polypeptides which are
designed to inhibit or mimic various GPRs or fragments thereof, as
receptor types and subtypes.

According to one aspect of the present invention, a synthetic or recombinant GPR polypeptide is provided that comprises a GPR amino acid sequence of, e.g., at least 5, 10, 15 or 20 amino acids, substantially corresponding to at least one transmembrane domain, or fragment and/or consensus peptide thereof, of a G-protein coupled receptor, wherein at least 20 amino acids are preferred. In a preferred embodiment, the polypeptide is (a) chemically synthesized and/or (b) obtained from a recombinant host cell or organism which expresses a recombinant nucleic acid encoding a GPR polypeptide, as defined herein.

In another preferred embodiment, the transmembrane domain is selected from at least one of TM1, TM2, TM3, TM4, TM5, TM6 or TM7, corresponding to transmembrane domains I, II, III, IV, V, VI and VII, respectively, of a GPR. In another preferred embodiment, the transmembrane domain is a dopamine receptor transmembrane domain selected from the group consisting of at least one of a D_1 , D_2 , D_3 , and D_4 dopamine receptor transmembrane domain. The

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preferred embodiment, the GPR polypeptide amino acid sequence

substantially corresponding to an amino acid sequence contained in at least one of Fig. 2 (SEQ ID NO:2), Fig. 3 (SEQ ID NO:3) or Fig. 5 (SEO ID NO:5).

In another aspect of the present invention, a GPR composition is provided, comprising a GPR polypeptide, or a pharmaceutically acceptable ester, ether, sulfate, carbonate, malate, glucuronide or salt thereof, the composition further comprising a pharmaceutically acceptable carrier and/or diluent.

In still another aspect of the present invention, a

method is provided for treating a subject suffering from a disease
state involving a qualitative or quantitative pathological
abnormality of a GPR protein or a biological molecule functionally
associated therewith. Such biological molecule may be a membrane
cytoplasmic protein, lipid, carbohydrate, saccharide, nucleoside

or nucleotide mono-, di-, or tri-phosphate, an enzyme, a cofactor, a nucleic acid, a neurotransmitter, an ion, a carrier, a
cell receptor, or any combination thereof.

In a preferred embodiment, the GPR protein is a dopamine receptor and the abnormality involves a dopamine related

20 pathology, wherein the method comprises administering an effective dopamine receptor modulating amount of a GPR polypeptide of the present invention. In another preferred embodiment, the transmembrane domain is a D₂ dopamine receptor domain and the disease state is a psychiatric disorder, such as schizophrenia or schiz affective disorder (see American Psychiatric Association, Revised Manual of Diagnostic and Statistical Criteria for Psychiatric Disorders (DSM-III-R), American Psychiatric Assoc.

Press, Washington, DC (1989)).

In another preferred embodiment, the GPR composition is administered as a pharmaceutical composition to provide a GPR polypeptide in an amount ranging from about 0.01 µg to 100 mg/kg, and also preferably, about 10 µg to 10 mg/kg. In another preferred embodiment, the administering is by oral, intravenous, intramuscular, parenteral or topical administration, including mucosal administration to the nasal mucosa or the oral mucosa, by aerosol, nebulizer or drop administration as non-limiting examples.

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Other objects of the invention will be apparent to skilled practitioners from the following detailed description and examples relating to the present invention.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is the amino acid sequence of a control peptide (SEQ ID NO:1), which is hydrophobic in its properties, but does not correspond to a known GPR transmembrane domain.

- Fig. 2 represents the amino acid sequence of a GPR transmembrane polypeptide, polypeptide II (SEQ ID NO:2), which corresponds to a portion of the dopamine D_2 receptor transmembrane segment III.
 - Fig. 3 represents the amino acid sequence of a transmembrane polypeptide, polypeptide III (SEQ ID NO:3), corresponding to a consensus peptide of the dopamine D_2 receptor transmembrane domains I-VII.
 - Fig. 4 represents the amino acid sequence of a consensus sequence of transmembrane domains that is shortened to be less than the length required to span a lipid bilayer.
- Fig. 5 represents a consensus amino acid sequence of transmembrane domain as a consensus peptide between dopamine receptors D_1 and D_2 .
 - Fig. 6 is a representation of a circular dichroism spectrum of a solution of the consensus polypeptide III (SEQ ID NO:3) of Fig. 3.
 - Fig. 7 is a graphical representation of radioligand binding assay data comparing control polypeptide II (SEQ ID NO:1) of Fig. 1, labeled as "II" and consensus polypeptide I (SEQ ID NO:3) of Fig. 3, labeled as "I".
- Fig. 8A-G are a comparison listing of amino acid sequences of transmembrane domains and adjacent amino acid sequences of representative GPRs (SEQ ID NOS:6-79).

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DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention relates to G-protein coupled receptor (GPR) polypeptides which can be used to mimic naturally occurring or isolated GPRs, or to modulate the binding of GPR ligands to GPRs, such as inhibition or enhancement of binding. GPR polypeptides of the present invention can include GPR transmembrane domain fragments and/or consensus peptides thereof, of at least 4-10 amino acids in length, and/or corresponding sequences having conservative amino acid substitutions as

10 "substitution peptides", wherein the GPR polypeptide binds a GPR ligand or modulates the binding of a GPR ligand to a GPR in vitro, in vivo or in situ.

GPR polypeptides of the present invention can be synthesized or recombinantly produced, or optionally purified, to provide commercially useful amounts of GPR polypeptides for use in therapeutic, diagnostic or research applications, according to known method steps, see, e.g., Ausubel et al, eds. Current Protocols in Molecular Biology, Wiley Interscience, N.Y., (1987, 1992); and Sambrook et al, Molecular Cloning, A Laboratory Manual, 2nd edition, Vols. 1-3, Cold Spring Harbor Press, (1989), which references are herein entirely incorporated by reference.

Additionally, GPR polypeptides according to the present invention can be used to generate polyclonal and/or monoclonal antibodies, anti-idiotype antibodies thereto, or fragments thereof, which may used for diagnostic and/or therapeutic applications, according to known method steps, see, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Press (1988), which is herein entirely incorporated by reference.

antibodies (or fragments thereof) to GPR polypeptides have been unexpectedly discovered to quantitatively or qualitatively modulate G-protein coupled receptors, such that binding of GPR polypeptides or anti-idiotype antibodies (or fragments thereof) to G-protein coupled receptor ligands may be used for diagnostic research or therapeutic applications of the present invention. Such GPR polypeptides, antibodies or anti-idiotype antibodies of the present invention may therefore be used as modulators of

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G-protein coupled receptors, such as neuroreceptors or endocrine receptors, as non-limiting examples.

Binding of such GPR polypeptides, (including GPR fragments, consensus peptides, substitution derivatives and anti-5 idiotype antibody fragments) of the present invention may be used to treat symptoms of, and provide diagnosis and treatment for, pathologies related to GPRs. Such pathologies have been found to correlate with symptoms occurring in neurological, viral or endocrine pathologies. D_2 receptor-related psychotic disorders, including schizophrenia, now treated with neuroleptics, is a nonlimiting example thereof.

The use of synthetic or recombinant GPR polypeptides of the present invention can be preferable to the use of known drugs that bind G-protein coupled receptors, such as neuroleptics that bind or inhibit the biological effect of binding to neuroreceptors 15 as a non-limiting example. Such polypeptides are expected to have significantly less side effects than presently used drugs presently used for inhibiting such receptor binding including neuroleptics, as they would structurally mimic naturally occuring GPRs and/or modulate ligand binding. Thus, GPR polypeptides are 20 expected to have reduced side effects attributable to known foreign compound drugs, with less immunogenicity, and reduced potential for motoric side effects (e.g., extrapyramidal symptoms and/or tardive dyskinesia).

25 The present invention is also related to the production, by chemical synthesis or recombinant DNA technology, of GPR polypeptides, preferably as small as possible while still retaining sufficiently high affinity or interaction with G-protein coupled receptors to modulate, such as to inhibit or to enhance, 30 binding to such receptors by GPR ligands.

GPR polypeptides of the present invention may include 5-10 to 50-150 amino acid fragments, consensus sequences or substitution sequences of GPRs, e.g., as presented in Fig. 8A-G (SEO ID NOS-6.70) including but her literated to morning

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thrombin receptors, kinin receptors, follicle stimulating hormone receptors, opsins and rhodopsins, odorant receptors, cytomegalovirus GPRs, adenosine A2 receptors, dopamine receptor, histamine H2 receptors, octopanmine receptors, N-formyl receptors, 5 anaphylatoxin receptors, thromboxane receptors, IL-8 receptors, platelet activating factor receptors, endothelin receptors, bombesin gastrin releasing peptide receptor, neuromedin B preferring bombesin receptors, vasoactive intestinal peptides, neurotensin receptors, bradykinin receptors, thyrotropin-releasing 10 hormone receptors, substance P receptors, neuromedin K receptors, adrenal angiotensen II type I receptors, mas oncogene (angiotensin) receptors lutropin-choriogonadotropin receptors, thyrotropin receptors, follicle stimulating hormone receptors, cannabinoid receptors, glucocorticoid-induced receptors, endothelial cell GPRs, testis GPRs, and thoracic aorta GPRs, and homologs thereof having a homology of at least 80% with at least one of transmembrane domains 1-7, as described herein. See, e.g., Probst et al DNA and Cell Biology 11:1-20(1992), which is entirely incorporated herein by reference.

Accordingly, a "G-protein coupled receptor polypeptide" or "GPR polypeptide" of the present invention includes polypeptides having a "GPR amino acid sequence" which substantially corresponds to at least one 10 to 50 amino acid fragment and/or consensus sequence of a known GPR or group of GPRs, wherein the GPR polypeptide has homology of at least 80%, such as 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% homology, while maintaining GPR modulating activity, wherein a GPR polypeptide of the present invention is not naturally occurring or is naturally occurring but is in a purified or isolated form which does not occur in nature. Preferably, a GPR polypeptide of the present invention substantially corresponds to a transmembrane domain of a GPR or group of GPRs as a consensus sequence.

Also preferred are GPR polypeptides wherein the GPR amino acid sequence is 4-10 to 50 amino acids in length, such as 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 0, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39,

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40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140 or 150 amino acids, or any range therein.

An amino acid or nucleic acid sequence of a GPR polypeptide of the present invention is said to "substantially 5 correspond" to another amino acid or nucleic acid sequence, respectively, if the sequence of amino acids or nucleic acid in both molecules provides polypeptides having biological activity that is substantially similar, qualitatively or quantitatively, to the corresponding fragment of at least one GPR transmembrane domain, or which may be synergistic when two or more transmembrane domains, consensus sequences or homologs thereof are present.

Additionally or alternatively, such "substantially corresponding" sequences of GPR polypeptides include conservative amino acid or nucleotide substitutions, or degenerate nucleotide codon substitutions wherein individual amino acid or nucleotide substitutions are well known in the art.

Alternatively or additionally, substantially corresponding refers to GPR polypeptides having amino acid sequences having at least 80% homology or identity to an amino acid sequence of SEQ ID NO:1, such as 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% homology or identity.

Accordingly, GPR polypeptides of the present invention, or nucleic acid encoding therefor, include a finite set of 25 substantially corresponding sequences as substitution peptides or polynucleotides which can be routinely obtained by one of ordinary skill in the art, without undue experimentation, based on the teachings and guidance presented herein. For a detailed description of protein chemistry and structure, see Schulz, G.E. 30 et al., Principles of Protein Structure, Springer-Verlag, New York, 1978, and Creighton, T.E., Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, 1983, which are hereby incorporated by reference. For a presentation of nucleatide sequence substitutions such as codor proformance

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Conservative substitutions of a GPR polypeptide of the present invention includes a variant wherein at least one amino acid residue in the polypeptide has been conservatively replaced by a different amino acid. Such substitutions preferably are made in accordance with the following list as presented in Table IV, which substitutions may be determined by routine experimentation to provide modified structural and functional properties of a synthesized polypeptide molecule, while maintaining the receptor binding, inhibiting or mimicking biological activity, as determined by known GPR receptor activity assays.

Table IV

Original Residue	Exemplary Substitution
Ala	Gly;Ser
Arg	Lys
Asn	Gln;His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Ala;Pro
His	Asn;Gln
Ile	Leu; Val
Leu	Ile;Val
Lys	Arg;Gln;Glu
Met	Leu; Tyr; Ile
Phe	Met; Leu; Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp; Phe
Val	Ile;Leu

Alternatively, another group of substitutions of GPR polypeptides of the present invention are those in which at least one amino acid residue in the protein molecule has been removed and a different residue inserted in its place according to the following Table V. The types of substitutions which may be made in the protein or peptide molecule of the present invention may be based on analysis of the frequencies of amino acid changes between a homologous protein of different species, such as those presented in Table 1-2 of Schulz et al., supra and Figs. 3-9 of Creighton, supra.

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Based on such an analysis, alternative conservative substitutions are defined herein as exchanges within one of the following five groups:

TABLE V

- Small aliphatic, nonpolar or slightly polar residues: Ala, Ser, 1. Thr (Pro, Gly);
- Polar, negatively charged residues and their amides: Asp, Asn, 2. Glu, Gln;
- 3. Polar, positively charged residues:
 - His, Arg, Lys;

activity, e.g. in receptor binding assays.

- Large aliphatic, nonpolar residues: Met, Leu, Ile, Val (Cys); and Large aromatic residues: Phe, Tyr, Trp.

The three amino acid residues in parentheses above have special roles in protein architecture. Gly is the only residue lacking any side chain and thus imparts flexibility to the chain. This however tends to promote the formation of secondary structure 5 other than α -helical. Pro, because of its unusual geometry, tightly constrains the chain. It generally tends to promote β -turn-like structures, although in some cases Cys can be participating in disulfide bond formation which is important in protein folding. Note the Schulz et al. would merge Groups 1 and 2, Note also that Tyr, because of its hydrogen bonding potential, has significant kinship with Ser, and Thr, etc.

Conservative amino acid substitutions according to the present invention, e.g., as presented above, are known in the art and would be expected to maintain biological and structural properties of the polypeptide after amino acid substitution. Most deletions and insertions, and substitutions according to the present invention are those which do not produce radical changes in the characteristics of the protein or peptide molecule. "Characteristics" is defined in a non-inclusive manner to define both changes in secondary structure, e.g. lpha-helix or eta-sheet, as well as changes in physiological

However, when the exact effect of the substitution, deletion, or insertion is to be confirmed one skilled in the art will appreciate that the effect of the substitution or substitutions will be evaluated by routine screening assays, either immunoassays or

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Maranges et al., eds., for example, a substituted polypeptide

typically is made by site-specific mutagenesis of the peptide molecule-encoding nucleic acid, expression of the mutant nucleic acid in recombinant cell culture, and, optionally, purification from the cell culture, for example, by immunoaffinity chromatography using a specific antibody on a chemically derivatized column or immobilized membranes or hollow fibers (to absorb the mutant by binding to at least one epitope).

A preferred use of this invention is the production, by chemical or recombinant DNA technology, of GPR polypeptides, 10 preferably as small as possible while still retaining sufficiently high affinity for binding to, or association with, GPRs. production of GPR polypeptides including smaller fragments or variants of such transmembrane domains, one skilled in the art, using known binding and inhibition assays, can readily identify the GPR 15 polypeptides capable of binding minimizing or modulating G-protein coupled receptors using known methods. Non-limiting examples of fragments of GPRs to be used as GPR polypeptides or as a basis for consensus sequences thereof for GPR polypeptides, are presented in Figs. 2-5 and Fig. 8A-G, wherein fragments or consensus sequences of 10 to 50 amino acids of at least one sequence of Figs. 2-5 or 20 corresponding to at least one transmembrane domain or domains 1-7 listed in Fig. 8A-G (SEQ ID NOS:6-79) are encompassed by the present invention, such as at least one transmembrane domain of one or more GPRs, such as a cAMP receptor (1), adenosine receptors (2-3); 25 muscarinic acetylcholine receptors (4-8); human adrenergic receptors (9-11, 14-16, 19-25, 28); adrenergic receptors (9-28); human thrombin receptor (31); endothelin receptors (35-36), bombesin receptors (37-38), endocrine receptors (48-50), rhodopsin (51). opsins (52-54), odorant receptors (55-64), and cytomegalovirus GPRs (72-54), as nonlimiting examples, wherein ("#") refers to the listed sequences in Fig. 8A-G.

Accordingly, GPR polypeptides may include consensus sequences and/or fragments of at least one of transmembrane domain 1-7 of one or more GPRs as presented in Figs. 2-5 (SEQ ID NO:2-5) or Fig. 8A-G. (SEQ ID NOS:6-79) or homologs thereof, which GPR polypeptides do not occur naturally, and/or which are provided in an isolated and/or purified form not found in nature.

Consensus peptides of GPR polypeptides of the present invention may include peptides which are distinct from known GPR sequences in critical structural features, but which are derived from consensus sequences of homologous GPR transmembrane domains 1-7, e.g., as presented in Fig. 8A-G (SEQ ID NOS:6-79). Such consensus peptides may be derived by molecular modeling, optionally combined with hydrophobicity analysis and/or fitting to model helices, as non-limiting examples. Such modeling can be accomplished according to known method steps using known modeling algorithms, such as, but not limited to, ECEPP, INSIGHT, DISCOVER, CHEM-DRAW, AMBER, FRODO and 10 Such algorithms compare transmembrane domains between CHEM-X. related G-protein coupled receptors, determine probable energymiminized structures and define alternative consensus polypeptide fragments.

Such consensus peptides or fragments of GPRs may then be synthesized or produced recombinantly, in order to provide GPR polypeptides according to the present invention which mimic, modulate or inhibit binding of ligands to G-protein coupled receptors. GPR ligands, in the context of the present invention, refer to biological molecules that bind GPRs in vitro, in situ or in vivo, and may include hormones, neurotransmitters, viruses or receptor binding domains, thereof, opsins, rhodopsins, nucleosides, nucleotides, coagulation cascade factors, odorants or pheremones, toxins, colony stimulating factors, platelet activating factors, neuroactive peptides, neurohumors, or any biologically active compounds, such as drugs or synthetic or naturally occurring compounds.

The following non-limiting examples of consensus peptides of GPRs of the present invention are provided by way of guidance and not by way of limitation. In GPR polypeptides of the present invention, one or more, preferably 4-10, Asp and/or Lys residues may additionally be incorporated at the carboxy and/or amino terminal ends in order to provide expected helix forming effects of the helix dipole effect, e.g., as described in Baldwin et al Biochem. 28:2130 (1989); Baldwin et al Proc. Nat'l Acad. Sci. USA 94.9998 (1982)

As a non-limiting example of GPR polypeptide of the present invention, dopamine receptor transmembrane fragments of transmembrane domain (e.g., domain III) as presented in Fig. 2 (SEO ID NO:2) or a consensus sequence as presented in Fig. 3 (SEO ID 5 NO:3), e.g., of D₂ domains I-VII. Additionally or alternatively a consensus sequence may include less than 20 amino acids, such as 15 amino acids corresponding to a transmembrane domain, such as a D, receptor domain, as presented in Fig. 4 (SEQ ID NO:4) as polypeptide IV, which is smaller than the length required by spanning an average lipid bilayer of a cell membrane.

However, in the context of the present invention, GPR polypeptides of greater than 15 -20 amino acids are preferred such that the GPR polypeptides are able to span the lipid bilayer.

Another non-limiting example of a GPR polypeptide using 15 dopamine receptor transmembrane domains is a consensus sequence of two or more GPR receptors, such as the dopamine D, and D, receptors. A non-limiting example of such a consensus GPR polypeptide is presented in Fig. 5 (SEQ ID NO:5).

Additionally, modified amino acids or chemical derivatives 20 of amino acids of consensus or fragments of GPRs proteins, according to the present invention may be provided, which polypeptides contain additional chemical moieties or modified amino acids not normally a part of the protein. Covalent modifications of the peptide are thus included within the scope of the present invention. 25 modifications may be introduced into a GPR polypeptide by reacting targeted amino acid residues of the polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or terminal residues. The following examples of chemical derivatives are provided by way of illustration and not by way of 30 limitation.

Aromatic amino acids may be replaced with D-L-naphylalanine, D- or L-Phenylglycine, D- or L-2-thieneylalanine, D- or L-1-, 2-, 3- or 4-pyreneylalanine, D- or L-3-thieneylalanine, D- or L-(2-pyridinyl)-alanine, D- or L-(3-pyridinyl)-alanine, D- or 35 L-(2-pyrazinyl)-alanine, D- or L-(4-isopropyl)-phenylglycine, D-(trifluoromethyl)-phenylglycine, D-(trifluoromethyl)-phenylalanine, D-p-fluorophenylalanine, D- or L-p-biphenylphenylalanine, D- or

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L-p-methoxybiphenylphenylalanine, D- or L-2-indole(alkyl)alanines, and D- or L-alkylainines where alkyl may be substituted or unsubstituted methyl, ethyl, propyl, hexyl, butyl, pentyl, isopropyl, iso-butyl, sec-isotyl, iso-pentyl, non-acidic amino acids, 5 of C1-C20.

Acidic amino acids can be substituted with non-carboxylate amino acids while maintaining a negative charge, and derivatives or analogs thereof, such as the non-limiting examples of (phosphono) alanine, glycine, leucine, isoleucine, threonine, or serine; or sulfated (e.g., -SO₃H) threonine, serine, tyrosine.

Other substitutions may include unnatural hyroxylated amino acids may made by combining "alkyl" (as defined and exemplified herein) with any natural amino acid. Basic amino acids may be substituted with alkyl groups at any position of the naturally occurring amino acids lysine, arginine, ornithine, citrulline, or 15 (guanidino)-acetic acid, or other (guanidino)alkyl-acetic acids, where "alkyl" is define as above. Nitrile derivatives (e.g., containing the CN-moiety in place of COOH) may also be substituted for asparagine or glutamine, and methionine sulfoxide may be substituted for methionine. Methods of preparation of such peptide derivatives are well known to one skilled in the art.

In addition, any amide linkage in any of the GPR polypeptides can be replaced by a ketomethylene moiety, e.g. (-C(=O)- CH_2 -) for (-(C=0)-NH-). Such derivatives are expected to have the 25 property of increased stability to degradation by enzymes, and therefore possess advantages for the formulation of compounds which may have increased in vivo half lives, as administered by oral, intravenous, intramuscular, intraperitoneal, topical, rectal, intraocular, or other routes.

In addition, any amino acid representing a component of the said peptides can be replaced by the same amino acid but of the opposite chirality. Thus, any amino acid naturally occurring in the L-configuration (which may also be referred to as the R or S,

TIME OF THE STATE OF THE SERVICE OF which can additionally be referred to as the R- or the S-, depending

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upon its composition and chemical configuration. Such derivatives have the property of greatly increased stability to degradation by enzymes, and therefore are advantageous in the formulation of compounds which may have longer *in vivo* half lives, when administered by oral, intravenous, intramuscular, intraperitoneal, topical, rectal, intraocular, or other routes.

Additional amino acid modifications of amino acids of GPR polypeptides of to the present invention may include the following: Cysteinyl residues may be reacted with alpha-haloacetates (and 10 corresponding amines), such as 2-chloroacetic chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteinyl residues may also be derivatized by reaction with compounds such as bromotrifluoroacetone, alpha-bromobeta-(5-imidozoyl)propionic acid, chloroacetyl phosphate, 15 N-alkylmaleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

Histidyl residues may be derivatized by reaction with compounds such as diethylprocarbonate e.g., at pH 5.5-7.0 because this agent is relatively specific for the histidyl side chain, and para-bromophenacyl bromide may also be used; e.g., where the reaction is preferably performed in 0.1 M sodium cacodylate at pH 6.0.

Lysinyl and amino terminal residues may be reacted with compounds such as succinic or other carboxylic acid anhydrides.

Derivatization with these agents is expected to have the effect of reversing the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include compounds such as imidoesters/e.g., as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate.

Arginyl residues may be modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin according to known method steps. Derivatization of arginine residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these

reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

The specific modification of tyrosyl residues <u>per se</u> is well-known, such as for introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. N-acetylimidizol and tetranitromethane may be used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

Carboxyl side groups (aspartyl or glutamyl) may be selectively modified by reaction with carbodiimides (R' N-C-N-R') such as 1-cyclohexyl-3-(2-morpholinyl- (4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4- dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues may be converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

15 Glutaminyl and asparaginyl residues may be frequently deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues may be deamidated under mildly acidic conditions. Either form of these residues falls within the scope of the present invention.

Derivatization with bifunctional agents is useful for 20 cross-linking the peptide to a water-insoluble support matrix or to other macromolecular carriers, according to known method steps. cross-linking agents include, Commonly used 1,1-bis(diazoacety1)-2-phenylethane, glutaraldehyde, 25 N-hydroxysuccinimide esters, for example, 4-azidosalicylic acid, homobifunctional imidoesters, including esters such disuccinimidyl a s dithiobis (succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents methyl-3-[(p-azidophenyl)dithio]propioimidateyieldphotoactivatable 30 intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates

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Other modifications of GPR polypeptides of the present invention may include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains (T.E. Creighton, Proteins: Structure and Molecule Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)), acetylation of the N-terminal amine, methylation of main chain amide residues (or substitution with N-methyl amino acids) and, in some instances, amidation of the C-terminal carboxyl groups, according to known method steps.

Such derivatized moieties may improve the solubility, absorption, permeability across the blood brain barrier biological half life, and the like. Such moieties or modifications of GPR polypeptides may alternatively eliminate or attenuate any possible undesirable side effect of the protein and the like. Moieties capable of mediating such effects are disclosed for example, in Remington's Pharmaceutical Sciences, 16th ed., Mack Publishing Co., Easton, PA (1980).

Such chemical derivatives of GPR polypeptides also may provide attachment to solid supports, including but not limited to, agarose, cellulose, hollow fibers, or other polymeric carbohydrates such as agarose, cellulose, such as for purification, generation of antibodies or cloning; or to provide altered physical properties, such as resistance to enzymatic degradation or increased binding affinity or modulation for GPRs, which is desired for therapeutic compositions comprising GPR polypeptides, antibodies thereto or fragments thereof. Such peptide derivatives are well-known in the art, as well as method steps for making such derivatives using carbodimides active esters of N-hydroxy succinimmide, or mixed anhydrides, as non-limiting examples.

Variation upon consensus peptide sequences of GPR polypeptide of the present invention may also include: the addition of one, two, three, four, or five lysine, arginine or other basic residues added to the -COOH terminal end of the peptide; and/or one, two, three, four, or five glutamate or aspartate or other acidic residues added to the amino terminal end of the peptide, where "acidic" and "basic" are as defined herein. Such modifications are

well known to increase the α -helical content of the peptide by the "helix dipole effect". They also can provide enhanced aqueous solubility of the peptide. See, e.g., Baldwin et al., <u>supra</u>

As another non-limiting example of a GPR polypeptide of the present invention, serotonergic receptors (5-HT) consensus sequences may be determined using presently known 5-HT sequences and include, e.g., as consensus peptides of TM3, TM5 and TM7, espectively:

- 5-HT consensus (1) DDDDNIWSIFDWIGYLNSISMVIYTLFKKKK (SEQ ID NO:80)
- 5-HT consensus (2) DDDDNIWNIFSTIGYLNSISPVSVIMHIYGKKKK (SEQ ID NO:81)
- 10 5-HT consensus (3) DDDDGYSIYDTLVTFAINPVYITVFKKKK (SEQ ID NO:82)

Such non-naturally occurring consensus sequences may also be further modified according to known method steps to provide additional consensus peptides with substituted amino acids to increase or decrease α -helical propensity and/or solubility (e.g., hydrophilicity). As a non-limiting example, 5-HT consensus peptide (1) above may be modified according to the present invention to have increase helical propensity and increased aqueous solubility as follows:

- 5-HT consensus (4) DDDDNAWSAFDWALYLNSISMAIYTYAKKKK (SEQ ID NO:83),
- wherein, e.g., smaller, non-polar residues replace either larger, more polar residues (e.g., Ala for Ile or Val) or larger aromatic residues (e.g., Ala for Phe).

Another non-limiting, illustrative example of consensus GPR polypeptides of the present invention are those for adrenergic receptors, are the following:

An example of the consensus GPR polypeptide for domain VII across all presently known adrenergic receptors is as follows:

adrenergic consensus(1) LFSFITWLGYANSSLNPIIYTTF (SEQ ID NO:84)

adrenergic consensus(2) VYTIYSSSVVFFAPSLAIMVITYT (SEQ ID NO:85)

Examples of a consensus GPR polypeptide for domain III across all adrenergic receptors are as follows:

adrenergic consensus(3) IWLTSDIMSTSSILHNLCVISF (SEQ ID NO:86)

An example of a consensus GPR polypeptide for domains III, V, and VII of all adrenergic receptors is as follows:

adrenergic consensus(4) IWSIFSSDIVVGYANHSSLAIMCPIVIYTV (SEQ ID NO:87)

adrenergic consensus(5) IFTIFSSDIAVGYANHSSAAIMPIVIYSV (SEQ ID NO:88),

Wherein variations and substitutions of amino acids may be made as 10 described herein.

Non-limiting examples of consensus GPR polypeptides for transmembrane domain III across several or many, such as 1-500, or any range or value therein, G-protein receptors are as follows:

- TM3-(1) YAIFVLYASAWLSFLNCPFIVTLNI (SEQ ID NO:96)
- 15 TM3-(2) YAIFVLYATAWLSFLNCPFIVTLNI(SEQ ID NO:97)
 - TM3-(3) YAIFVLYATAWLTFLNCPFIVTLNI(SEQ ID NO:98)
 - TM3-(4) YAIFVLYASAWLTFLNCPFIVTLNI(SEQ ID NO:99)
 - '1M3-(5) WAIFVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:100)
 - TM3-(6) WAIFVLYATAWLSFLNCPFIVTLNI(SEQ ID NO:101)
- 20 TM3-(7) WAIFVLYATAWLTFLNCPFIVTLNI(SEQ ID NO:102)
 - TM3-(8) WAIFVLYASAWLTFLNCPFIVTLNI(SEQ ID NO:103)
 - TM3-(9) YAVFVLYASAWLSFLNMPFIVTLNI(SEQ ID NO:104)
 - TM3-(10) YAVFVLYATAWLSFLNMPFIVTLNI(SEQ ID NG:105)
 - TM3-(11) YAVFVLYATAWLTFLNMPFIVTLNI(SEQ ID NO:106)
- 25 TM3-(12) YAVFVLYASAWLTFLNMPFIVTLNI(SEQ ID NO:107)
 - TM3-(13) YAIFVLYASAWLSFLNCVTASIPFIVTLNI(SEQ ID NO:108)
 - TM3-(14) YAIFVLYASAWLSFLNCTSSIVVTASIVTLNI(SEQ ID NO:109)
 - TM3-(15) YAIFVLYASAWLSFLNVTLNICTSSIV(SEQ ID NO:110)
 - TM3-(16) YAIFVLYASAWLSFLNTASILNIMFIVTLNI(SEQ ID NO:111)
- 30 TM3-(17) YAIFVLYASAWLSFLNMASILNLPFIVTLNI(SEQ ID NO:112)
 - TM3-(18) YAIFVLYASAWLSFLNSGILLLAPFIVTLNI(SEQ ID NO:113)
 - TM3-(19) YAIFVLYASAWLSFLNMSGILLLAPFIVTLNI(SEQ ID NO:114)
 - TM3-(20) YAIFVLYASAWLSFLNSELSVYTLTVCPFIVTLNI(SEQ ID NO:115)
 - TM3-(21) YAIFVLYASAWLSFLNMSELSVYTLTVPFIVTLNI(SEQ ID NO:116)

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TM3-(22) YAIFVLYASAWLASELSVYTLTVSFLNCPFIVTLNI(SEQ ID NO:117)
    TM3-(23) YAIFVLYASAWLASELSVYTLTVPFIVTLNI(SEQ ID NO:118)
    TM3-(24) YAIFVLYASAWLSFLASELSVYASELSSTLTTVNMPFIVTLNI(SEQ ID NO:119)
    TM3-(25) YAIFVLYASAWLSFLNGGEIALWSLCPFIVTLNI(SEQ ID NO:120)
 5 TM3-(26) YAIFVLYASAWLSFLNGGEIALWSLIVTLNI(SEQ ID NO:121)
    TM3-(27) YAIFVLYASAWLGGEIALWSLNCPFIVTLNI(SEQ ID NO:122)
    TM3-(28) YAIFVLYAGGEIALWSLSFLNCPFIVTLNI(SEQ ID NO:123)
    TM3-(29) YAIFVLYASAWLSFFFLLFGYLGNFLLNCPFIVTLNI(SEQ ID NO:124)
    TM3-(30) YAIFVLYASAWLFFFLLFGYLGNFLLPFIVTLNI(SEQ ID NO:125)
10 TM3-(31) YAIFVLYASAWLSFLNTACFYVAITASLCFITEIALIPFIVTLNI(SEQ ID NO:126)
    TM3-(32) YAIFVLYASAWLTACFYVAITASLCFITEIALICPFIVTLNI(SEQ ID NO:127)
    TM3-(33) YAIFVLYATACFYVAITASLCFITEIALISFLNCPFIVTLNI(SEQ ID NO:128)
    TM3-(34) YAITACFYVAITASLCFITEIALIASAWLSFLNCPFIVTLNI(SEO ID NO:129)
    TM3-(35) YAIFVLYATACFYVAIITEIALISAWLSFLNCPFIVTLNI(SEQ ID NO:130)
15 TM3-(36) YAIFVLYASAWLSFLNACFYICLFAGVCFLIPFIVTLNI(SEQ ID NO:131)
    TM3-(37) YAIFVLYASAWNACFYICLFAGVMFLILSFLNCPFIVTLNI(SEQ ID NO:132)
    TM3-(38) YAIFVLYFYICLFAGVCFLIASAWLSFLNCPFIVTLNI(SEQ ID NO:133)
    'TM3-(39) YAIFVLYASVDAVNMFTSAWLSFLNCPFIVTLNI(SEQ ID NO:134)
    TM3-(40) YAIFSVDAVNMFTVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:135)
20
   TM3-(41) YAIFVLYASAWLSVDAVNMFTSFLNCPFIVTLNI(SEQ ID NO:136)
    TM3-(42) YAIFVLYASAWLSFLNSVDAVNMFTPFIVTLNI(SEQ ID NO:137)
    TM3-(43) YAIFVLYASAWLSFLNCPFIVSVDAVNMFTTLNI(SEQ ID NO:138)
    TM3-(44) YAIFVLYASAWLSVDMFTSFLNCPFIVTLNI(SEQ ID NO:139)
    TM3-(45) YAISVDAVNMFTFVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:140)
25 TM3-(46) YAIFSLSVFSLLAIVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:141)
    TM3-(47) YAIFVLYASLSVFSLLAISAWLSFLNCPFIVTLNI(SEQ ID NO:142)
    TM3-(48) YAIFVLYASAWLSLSVFSLLAISFLNCPFIVTLNI(SEQ ID NO:143)
    TM3-(49) YAIFVLYASAWLSFLSLSVFSLLAINCPFIVTLNI(SEQ ID NO:144)
    TM3-(50) YAIFVLYASAWLSFLNPFSLSVFSLLAIIVTLNI(SEQ ID NO:145)
30 TM3-(51) YAIFVLYATAWLTFLNCVTATIPFIVTLNI(SEQ ID NO:146)
    TM3-(52) YAIFVLYATAWLSFLNCTSSIVVTATIVTLNI(SEQ ID NO:147)
    TM3-(53) YAIFVLYATAWLSFLNVTLNICTTTIV (SEQ ID NO:148)
    TM3-(54) YAIFVLYATAWLTFLNTATILNLMFIVTLNI(SEQ ID NO:149)
    TM3-(55) YAIFVLYATAWLSFLNMATILNLPFIVTLNI(SEQ ID NO:150)
35 TM3-(56) YAIFVLYATAWLTFLNSGILLLAPFIVTLNI(SEQ ID NO:151)
    TM3-(57) YAIFVLYASAWLTFLNMTGILLLAPFIVTLNI(SEQ ID NO:152)
    TM3-(58) YAIFVLYASAWLTFLNTELTVYTLTVCPFIVTLNI(SEQ ID NO:153)
    TM3-(59) YAIFVLYASAWLTFLNMTELTVYTLTVPFIVTLNI(SEQ ID NO:154)
    TM3-(60) YAIFVLYATAWLATELTVYTLTVTFLNCPFIVTLNI(SEQ ID NO:155)
4.0
   TM3-(61) YAIFVLYASAWLATELSVYTLTVPFIVTLNI(SEQ ID NO:156)
    TM3 - (62) YATEVLYATAWLSPLATELSVYASELSTTUUTVNMPPIVTUNT (SPO. TO NO LEG
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TM: 0: .AIFVLYASAWLAGETALWTLNCPFIVTLNI(SEQ IL NO:180

45 TM3-(66) YAIFVLYAGGEIALWTLSFLNCPFIVTLNI(SEQ ID NO:161)

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TM3-(67) YAIFVLYATAWLSFFFLLFGYLGNFLLNCPFIVTLNI(SEQ ID NO:162) TM3-(68) YAIFVLYATAWLFFFLLFGYLGNFLLPFIVTLNI(SEQ ID NO:163) TM3-(69) YAIFVLYATAWLTFLNTACFYVAITASLCFITEIALIPFIVTLNI(SEQ ID NO:164) TM3-(70) YAIFVLYATAWLTACFYVAITATLCFITEIALICPFIVTLNI (SEO ID NO:165) 5 TM3-(71) YAIFVLYATACFYVAITATLCFITEIALISFLNCPFIVTLNI(SEQ ID NO:166) TM3-(72) YAITACFYVAITASLCFITEIALIATAWLTFLNCPFIVTLNI(SEQ ID NO:167) 'TM3 - (73) YAIFVLYATACFYVAIITEIALITAWLTFLNCPFIVTLNI (SEO ID NO:168) TM3-(74) YAIFVLYASAWLTFLNACFYICLFAGVCFLIPFIVTLNI(SEQ ID NO:169) TM3-(75) YAIFVLYASAWNACFYICLFAGVMFLILTFLNCPFIVTLNI(SEQ ID NO:170) 10 TM3-(76) YAIFVLYFYICLFAGVCFLIATAWLTFLNCPFIVTLNI(SEQ ID NO:171) TM3-(77) YAIFVLYATVDAVNMFTTAWLTFLNCPFIVTLNI(SEO ID NO:172) TM3-(78) YAIFTVDAVNMFTVLYATAWLTFLNCPFIVTLNI(SEQ ID NO:173) TM3-(79) YAIFVLYATAWLTVDAVNMFTSFLNCPFIVTLNI(SEQ ID NO:174) TM3-(80) YAIFVLYATAWLSFLNIVDAVNMFTPFIVTLNI(SEQ ID NO:175) 15 TM3-(81) YAIFVLYASAWLTFLNCPFIVSVDAVNMFTTLNI(SEQ ID NO:176) TM3-(82) YAIFVLYATAWLSVDMFTTFLNCPFIVTLNI(SEQ ID NO:177) TM3-(83) YAISVDAVNMFTFVLYATAWLSFLNCPFIVTLNI(SEQ ID NO:178) TM3-(84) YAIFVLYASLTVFSLLAISAWLTFLNCPFIVTLNI(SEQ ID NO:179) TM3-(85) YAIFVLYASAWLTLSVFTLLAISFLNCPFIVTLNI(SEO ID NO:180) 20 TM3-(86) YAIFVLYASAWLTFLSLSVFTLLAINCPFIVTLNI(SEQ ID NO:181) TM3-(87) YAIFVLYASAWLTFLNPFSLSVFSLLAIIVTLNI(SEQ ID NO:182) TM3-(88) YAIFVLYASAWLSFLNLGGVTASFTASVGPFIVTLNI(SEQ ID NO:183) TM3-(89) YAIFVLYASAWLSFLNLGGVTASFTASVGVTLNI(SEQ ID NO:184) TM3-(90) YAIFVLLGGVTASFTASVNYASAWLSFLNCPFIVTLNI(SEQ ID NO:185) 25 TM3-(91) YAIFVLYAIFFFLLFSAWLSFLNCPFIVTLNI(SEQ ID NO:186) TM3-(92) YAIFVLYASAWLSFLNCPFIVTLNIIFFFLLFIVTLNI(SEQ ID NO:187) TM3-(93) YAIFVLYASAWIFFFLLFLSFLNCPFIVTLNI(SEQ ID NO:188) TM3-(94) YAIFVLYASAWLFFTVLASELSVYTLTVSFLNCPFIVTLNI(SEQ ID NO:189) TM3-(95) YAIFVLYASAWLSFLFATLGGEIALCPFIVTLNI(SEQ ID NO:190) 30 TM3-(96) YAIFVLYAFATLGGEIALSAWLSFLNCPFIVTLNI(SEQ ID NO:191) TM3-(97) YAIFFTVLASELSVYTLTVYASAWLSFLNCPFIVTLNI(SEQ ID NO:192) TM3-(98) YAIFFPIAALFASIASAWLSFLNCPFIVTLNI(SEQ ID NO:193) TM3-(99) YAIFVLYASAWLSFFPIAALFASIPFIVTLNI(SEQ ID NO:194) TM3-(100) YAIFVLYASAWLSFLNCPFFPIAALFASILNI(SEQ ID NO:195) 35 TM3-(101) YAIFVLYASAWLSLDVLFSTASIMHLSFLNGGEIALWSLIVTLNI(SEQ ID NO:196) TM3-(102) YAIFVLYASLDVLFSTASIMHLIALWSLNCPFIVTLNI(SEQ ID NO:197) TM3-(103) YAIFVLYAGGEIALWSLSFLNSLDVLFSTASIMHLPFIVTLNI(SEQ ID NO:198) TM3-(104) YAIFVLYASAWLSFFDVLFSTASIMHLFGYLGNFLLNCPFIVTLNI(SEQ ID NO:199) TM3-(105) YAIFVLYASAWLFFFLLFGYLSLDVLFSTASIMHLGNFLLPFIVTLNI(SEQ ID NO:200) 40 TM3-(106) YAIFVLYASAWLSFLNTACFYVAITASLSLMHLFITEIALIPFIVTLNI (SEQ ID NO:201) TM3-(107) YASLDVLFSTAIMHLSAWLTACFYVAITASLCFITEIALICPFIVTLNI(SEQ ID NO:202) TM3-(108) YAIFVLYATACFYVAITASLSFLNCPFIVTLNISLDVLFSTASIMHL(SEQ ID NO:203) TM3-(109) YAITACFYVAITASLCFITEIALIASAWLSFLNCPFIVTLNI(SEQ ID NO:204) TM3-(110) YAIFVLYATACFYSTASILNLIMHLCAISLVAIITEIALISAWLSFLN(SEQ ID NO:205) 45 TM3-(111) YAIFVLYASAWLSFLNACFYICLFASILNLIMHLGVCFLIPFIVTLNI(SEQ ID NO:206)

Profession A. A. Marie Marie

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TM3-(112) YAIFVLYASAWNASILNLIMHLCFYICLFAGVMLILSFLNCPFIVTLNI(SEQ ID NO:207)
     TM3-(113) YAIFPFVQCVVSIFSLVLIAVVLYFYIAGVCFLIASAWLSFLNCPFIVTI(SEQ ID NO:208)
     TM3-(114) PFVQCVSITVSIFSLVLIAVYAIFVLYASVDAVNMFTSAWCPFIVTLNI(SEQ ID NO:209)
    TM3-(115) YAIFGDWSSVDAVNMFTVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:210)
   TM3-(116) YAIFVLYAGDWSSAWLSVDAVNMFTSFLNCPFIVTLNI(SEQ ID NO:211)
    TM3-(117) YAIFVLYASAWLGDWSSFLNSVDAVNMFTPFIVTLNI(SEQ ID NO:212)
    TM3-(118) YAIFVLYASAWLSFLNCPFIVGDWSSVDAVNMFTTLNI(SEQ ID NO:213)
    TM3-(119) YAIFVLYASAWLGYLGSVDMFTSFLNCPFIVTGDWSLNI(SEQ ID NO:214)
    TM3-(120) YAISVDAVNMFTFVLYAGYLGSAWLSFLNCPFIVTLNI(SEQ ID NO:215)
10
   TM3-(121) YAIFSLSVFSLLAIVLYASAWLGYLGSFLNCPFIVTLNI(SEQ ID NO:216)
    TM3-(122) YAIFVLYAGYLGAGNMDSLSVFSLLAISAWLSFLNCPFIVTLNI(SEQ ID NO:217)
    TM3-(123) YAIFVLYASAWLSLSVFGNMSLLAISFLNCPFIVTLNI(SEQ ID NO:218)
    TM3-(124) YAIFVLYASAWLSFLSLSVFGGSLLAINCPFIVTLNI(SEQ ID NO:219)
    TM3-(125) YAIFVLYASAWLSFLNPFSLSVFGSLLAIIVTLNI(SEQ ID NO:220)
15 TM3-(126) YAIFVLYATAWLTFLSLANCVTATIPFIVTLNI(SEQ ID NO:221)
    TM3-(127) YAIFVLYATAWLSFLNCTSLASSIVVTATIVTLNI(SEQ ID NO:222;
    TM3-(128) YAIFVLYATAWLSFLNVTLNISLACTTTIV(SEQ ID NO:223)
    TM3-(129) YAIFVLYATAWLTFLNTATILSLANLMFIVTLNI(SEQ ID NO:224)
    TM3-(130) YAIFVLYATAWLSFLNMATILNLPFSVDAVIVTLNI(SEQ ID NO:225)
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Recently discovered G-proteins also can be used according to the presently claimed invention to provide GPR polypeptides of the present invention, based on the teaching and guidance presented herein. Exampled of such GPR polypeptides of the present invention may include, as non-limiting examples, GPR polypeptides corresponding to transmembrane domain III, e.g., as follows:

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TM3-(131) ISTMYTVTGRWTLGQVVCDFWLSSDITCCTASILHLCVIAL (SEQ ID NO:226)
TM3-(132) ILYGYRWPLPSKLCAVWIYLDVLFSTASIMHLCAISL (SEQ ID NO:227)
TM3-(133) IIYI VMDRWKLGYFLCEVWLSVDMTCCTCSILHLCVIAL (SEQ ID NO:228)
TM3-(134) IADKTVRVAMGAENDLGYNFRSDDVCGHCWQWYCSL (SEQ ID NO:229)
30 TM3-(135) ILNYWPFGLALCHFVNYSQAVSVLVSAYTLVAISI (SEQ ID NO:230)
TM3-(136) ILGRWEFGIHLCKLWLTCDVLCCTSSILNLCAIALD (SEQ ID NO:231)
TM3-(137) IMASVMHRHCLPLIGICLSSERHCLVSIFVELGAL (SEQ ID NO:232)
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Further non-limiting examples of consensus GPR polypeptides for transmembrane domain III of several or many, such as 1-500, or any range or value therein, more recently discovered G-protein

TM3-(139) YAIFVLYATAWLSFLNCPFISILNLCAIALDVTLNI(SEQ ID NO:234)

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TM3-(140) YAIFVLYATAWLTFLNCPFISIFVELGALVTLNI(SEQ ID NO:235) TM3-(141) YAIFVLYASAWLTFLNCPFISIFVELSIMHLCAISLGALVTLNI(SEQ ID NO:236) TM3-(142) WAIFVLYAILGRWEFGIHLCKLWLTSAWLSIMHLCAISLSFLNCPFIVTLNI(SEQ ID NO:237) TM3-(143) WAIFVLYAILGRWEFGIHLCKLWLTTAWLSIMHLCAISLSFLNCPFIVTLNI(SEQ ID NO:238) 5 TM3-(144) WAIFVLYATAWLTFLNCPFSIMHLCAISLIVTLNI(SEQ ID NO:239) TM3-(145) WAIFVLYASAWLTFLNCPFISIMHLCAISLVTLNI(SEQ ID NO:240) TM3-(146) YAVFVLYASAWLSFLNMSIMHLCAISLPFIVTLNI(SEQ ID NO:241) TM3 - (147) YAVFVLYATAWLSFLNMPFSILNLCAIALDIVTLNI (SEQ ID NO:242) TM3-(148) YAVFVLYATAWLSILNLCAIALDTFLNMPFIVTLNI(SEQ ID NO:243) 10 TM3-(149) YAVFVLYASILNLCAIALDSAWLTFLNMPFIVTLNI(SEQ ID NO:244) TM3-(150) YAIFVLYASAWLSFLNCVTASIPFCLVSIFVELGALIVTLNI(SEQ ID NO:245) TM3-(151) YAIFVLYASAWLSFLNCLVSIFVELGALIVVTASIVTLNI(SEQ ID NO:246) TM3-(152) YAIFVLYASAWLSFLNVTLNCLVSIFVELGALII(SEQ ID NO:247) TM3-(153) YAIFVLYASAWLSFLNTASILNLMFICLVSIFVELGALVTLNI(SEQ ID NO:248) 15 TM3-(154) YAIFVLYASAWLSFLNMASILNLPFCLVSIFVELGALVTLNI(SEQ ID NO:249) TM3-(155) YAIFVLYASAWLSFLNILGRWEFGIHLCKLWLTCDVLCCTSSGILLLAPFIVTLNI(SEQ ID NO:250) TM3-(156) YAIFVLYASAWLSFLNMILGRWEFGIHLCKLWLTCDVLCCTSSGILLLAPFIVTLNI(SEQ ID NO:251) TM3-(157) YAIFVLYASAWLILGRWEFGIHLCKLWLTCDVLCCTSSFLNSELSVYTLTVCPFIVTLNI (SEQ ID NO:252) 20 TM3-(158) YAIFVLYAILGRWEFGIHLCKLWLTCDVLCCTSSAWLSFLNMSELSVYTLTVPFIVTLNI(SEQ ID NO:253) TM3-(159) YAIFVLYASAWLASRWPLPLSVYTLTVSFLNCPFIVTLNI(SEQ ID NO:254) TM3-(160) YAIFVLYASAWLASELILYYWRWPLPCLHDLVWLCTCSILHLCVIALSV/TLTVPFIVTLNI(SEO ID NO:255) 25 TM3-(161) YAIFVLYASAWLSFLASELSVYASELSSTLHDLVWLWLDVFCVIALTTVNMPFIVTLNI(SEQ ID NO:256) TM3-(162) YAIFVLYASAWLSFLNGGEIALWSLCPFIILYYWRWPLPCLHDLVSILHLCVIALVTLNI(SEQ ID NO:257) TM3-(163) YVWLWLDVFCCTCSILHLCVIALFVLYASAWLSFLNGGEIALWSLIVTLNI(SEQ ID NO:258) 30 TM3-(164) YAIFVLYASAWLAIILYYWRWPLPCLHDLGGEIALWSLNCPFIVTLNI(SEQ ID NO:259)

Non-limiting examples of consensus GPR polypeptides for domain V across several or many, such as 1-500, or any range or value therein, G-protein receptors are as follows:

- TM5-(1) CDVFVFVDIMLCTASIFNLCAISVG(SEQ ID NO:260)
- 35 TM5-(2) YAIFVLYDIMLCTASIFNLCAISVG(SEQ ID NO:261)
 - TM5-(3) DYAIFVFVDIMLMTASIFNLMAISVG(SEQ ID NO:262)
 - TM5-(4) DYAIFVFVDIMLHTTASTIFNLMATITVG(SEQ ID NO:263)
 - TM5-(5) CDVAVVYSSDIMLFYVCTASIFSSNLCAISSVG(SEQ ID NO:264)
 - TM5-(6) FLFCSLGSFYIPIAVILVDIMLCTASIFNLCAISVG(SEQ ID NO:265)
- 40 TM5-(7) YAIFVLYDFLFCSLGSFYIPIAVILIMLCTASIFNLCAISVG(SEQ ID NO:266)
 - TM5-(8) DYAIFVFVDIMLMTASIFLFCSLGSFYIPIAVILISVG(SEQ ID NO:267)
 - TM5-(9) DYAIFVFVDIMLHTTASTIFNLMAFLFCSLGSFYIPIAVILTITVG(SEQ ID NO:268)

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TM5-(10) CDVAVVYSSDIMLFYVCTASIFSSNLFLFCSLGSFYCAISSVG(SEQ ID NO:269)
     TM5-(11) CDVFVFVDIMLCTASIFNWYILSSIGSFFAPCLILLVYLLCAISVG(SEQ ID NO:270)
    TM5-(12) YAIFVLYDIMLCTASIFNLCAIWYILSSIGSFFAPCLILLVYLSVG(SEQ ID NO:271)
    TM5-(13) DYAIFVFVDIWYILSSIGSFFAPCLILLVYLASIFNLMAISVG(SEQ ID NO:272)
 5 TM5-(14) DYAIWYILSSIGSFFAPCLILLVYLIMLHTTASTIFNLMATITVG(SEQ ID NO:273)
    TM5-(15) CDVAVVYSSDIMLFYVCWYILSSIGSFFAPCLILLVYLSSNLCAISSVG(SEQ ID NO:274)
    TM5-(16) CDVFVFVDIMLCTASIFWYVISSSIGSFFAPCLINHLVYNLCAISVG(SEQ ID NO:275)
    TM5-(17) YAIFVLYDIMLCTASIFNLCAIWYVISSSIGSFFAPCLINHLVYSVG(SEQ ID NO:276)
    TM5-(18) DYAIFVFVWYVISSSIGSFFAPCLINHLVYDIMLMTASIFNLMAISVG(SEQ ID NO:277)
10 TM5-(19) DYAIFVFVDIMLHTTASTIFWYVISSSIGSFFAPCLINHLVYTVG(SEQ ID NO:278)
    TM5-(20) CDVAVVYSSDIMLFYVCTASIFSWYVISIGSFFAINHLVYNLCAISSVG(SEQ ID NO:279)
    TM5-(21) CDVFVFVDIMLCTASIFNLCAITYAISSSVISFYIPVAILVTYT(SEQ ID NO:280)
    TM5-(22) YAIFVLYDIMLCTATYAISSSVISFYIPVAILVTYTSIFNLCAISVG(SEQ ID NO:281)
    TM5-(23) DYAIFVFVDIMLMTATYAISSSVISFYIPVAILVTYTISVG(SEQ ID NO:282)
15 TM5-(24) TYAISSSVISFYIPVATDYAIFVFVDIMLHTTASTIFNLMATITVG(SEQ ID NO:283)
    TM5-(25) CDVAVVYSSDIMLFYVCTATYAISSSVISFYIPVAILVTYTSSVG(SEQ ID NO:284)
    TM5-(26) CDVFVFVDFVIYSSVVSFYLPFGVTVLVYACTASIFNLCAISVG(SEQ ID NO:285)
    TM5-(27) YAIFVLYDFVIYSSVVSFYLPFGVTVLVYASIFNLCAISVG(SEQ ID NO:286)
    TM5-(28) DYAIFVFVDFVIYSSVVSFYLPFGVTVLVYATASIFNLMAISVG(SEQ ID NO:287)
20 TM5-(29) DYAIFVFVDFVIYSSVVSFYLPFGVTVLVYAHTTASTIFNLMATITVG(SEQ ID NO:288)
    TM5-(30) CDVAVVYSSDFVIYSSVVSFYLPFGVTVYVCTASIFSSNLCAISSVG(SEQ ID NO:289)
    TM5-(31) CDVFVFVDIMLCTASYTIYSTCGAFYIPSVLLIILYGNLCAISVG(SEQ ID NO:290)
    TM5-(32) YAIFVLYDIMLCTASYTIYSTCGAFYIPSVLLIILYGNLCAISVG(SEQ ID NO:291)
    TM5-(33) DYAIFVFVDIMLMTASYTIYSTCGAFYIPSVLLIILYGNLMAISVG(SEQ ID NO:292)
25 TM5-(34) DYAIFVFVDIMLHTTASYTIYSTCGAFYIPSVLLIILYGMATITVG(SEQ ID NO:293)
    TM5-(35) CDVAVVYSSDIMSYTIYSTCGAFYIPSVLLIILYGIFSSNLCAISSVG(SEQ ID NO:294)
    TM5-(36) CDVFVFFVLIGSFVAVDIMLCTASIFNLCAISVG(SEQ ID NO:295)
    TM5-(37) YAIFVLYFVLIGSFVADIMLCTASIFNLCAISVG(SEQ ID NO:296)
    TM5-(38) DYAIFVFVFVLIGSFVADIMLMTASIFNLMAISVG(SEQ ID NO:297)
30 TM5-(39) DYAIFVFVFVLIGSFVADIMLHTTASTIFNLMATITVG(SEQ ID NO:298)
    TM5-(40) CDVAVVYSSFVLIGSFVADIMLFYVCTASIFSSNLCAISSVG(SEQ ID NO:299)
    TM5-(41) CDVFVFVDIMLCFFIPTLIMVITYFNLCAISVG(SEQ ID NO:300)
    TM5-(42) YAIFVLYDIMLCFFIPTLIMVITYFFNLCAISVG(SEQ ID NO:301)
    TM5-(43) DYAIFVFVDIMLMFFIPTLIMVITYFNLMAISVG(SEQ ID NO:302)
35 TM5-(44) DYAIFVFVDIMLHTFFIPTLIMVITYFNLMATITVG(SEQ ID NO:303)
    TM5-(45) CDVAVVYSSDIMLFYVCFFIPTLIMVITYFSSNLCAISSVG(SEQ ID NO:304)
    TM5-(46) CDVVYGLVDGLVTFYLPLLIMCITYYDIMLCTASIFNLCAISVG(SEQ ID NO:305)
    TM5-(47) YAIVYGLVDGLVTFYLPLLIMCITYYDIMLCTASIFNLCAISVG(SEQ ID NO:306)
    TM5-(48) DYAIVYGLVDGLVTFYLPLLIMCITYYDIMLMTASIFNLMAISVG(SEQ ID NO:307)
   TM5-(49) DYAIVYGLVDGLVTFYLPLLIMCISSDIMLHTTASTIFNLMATITVG(SEQ ID NO:308)
40
             AIPVIYDIMLEVIRIGHVIVII FULIIUSYAIFNEGAISWOORQUU Ngaar
    TM5-(53) DYAIFVFVDIMLMLVIFLGLVIVIPFVLIIVSYAIFNLMAISVG(SEQ ID NO:312)
45 TM5-(54) DYAIFVFVDIMLHTLVIFLGLVIVIPFVLIIVSYAIFNLMATITVG(SEQ ID NO:313)
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	TM5 - (55) CDVAVVYSSI	IMLFLVIFLGLVIV	IPFVLIIVSYAIFS	SSNLCAISSVG (Sa	O ID NO:314)	
	TM5-(56) CDVFVFVDIN					
	TM5-(57) YAIFVLYDIN					
	TM5-(58) DYAIFVFVDI					
5	TM5-(59) DYAIFVFVDI					
	TM5-(60) CDVAVVYSSE					
	TM5-(61) CDVFVFVDIM					
	TM5-(62) YAIFVLYDIM					
	TM5-(63) DYAIFVFVDI					
10	TM5-(64) DYAIFVFVDI					
	TM5-(65) CDVAVVYSSD					
	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	The state of the s	VIIIVIPFV	LIVISIAAISSVG	(2FO ID MO:32	4)
	Non-li	miting exampl	es of longe	r consensus	CDP polime	
	for domain V acr					
					or any va.	lue or
	range therein, G	-protein rec	eptors are	as follows:		
15	T M	1	-	(1)
	TM1NWPALSIVVIIINTIG			ISLFVLIGSFVAF	FIPLTIMVITYFL	FNVFFVV
	IGYVCSSSLGINPVIIYTL	F(SEQ ID NO:325)			
	T M	1	-	(2)
	NWPALSIVVIIINTIGGNI		LCTATILNLLISL	FVLIGTFVAFFIPI	TIMVITYFLFNV	FFVWIGY
20	VCTTTLGINPVIIYTLF(S	EQ ID NO:326)				
	T M	1	-	(3)
	NWPALTIVVIIINTIGGNI	LVIMAVSIYTTLDVM	LCTATILNLLITL	FVLIGTFVAFFIPI	TIMVITYFLFNV	FFVWIGY
	VCSTSLGINPVIIYTLF(S	EQ ID NO:327)				
	T M	1	-	(5)
25	NWPALTIVVIIINTIGGNI	LVIMAVTIYTTLDVM	LCTATILNLLITL	FVLIGTFVAFFIPI	TIMVITYFLFNVI	FFVWIGY
	VCTLGINPVIIYTLF (SEQ	ID NO:328)				
	T M	1	-	(6)
	NWKNWSALLTTVVIILTIA	GNILVIMAVSSLDVM	LCTASILNLLISL	FVLIGSFVAFFIPL	TIMVITYFLFNVI	FFVWIGY
	VCSSSLGINPVIIYTLF(S	EQ ID NO:329)				
30	T M	1	-	(7)
	ITITVVLAVLILITVAGNV	VVCIAVGSIYTSLDV	MLCTASILNLLIS:	LFVLIGSFVAFFIP	LTIMVITYFLFM	VFFVWIG
	YVCSSSLGINPVIIYTLF(SEQ ID NO:330)				
	T M	1	-	(8)
	TLTLVCIACLUSLTVFGNV	LVIIAVFSLDVMLCT	ASILNLLISLFVL:	IGSFVAFFIPLTIM	VITYFLFNVFFV	#IGYVCS
35	SSLGINPVIIYTLF (SEQ					
	T M	1	-	(9)
	TAAIAAAITFLILFTIFGN	ALVIIAVLSIYTSLD	VMLCTASILNLLI	SLFVLIGSFVAFFI	PLTIMVITYFLFN	VFFVWI
	GYVCSSSLGINPVIIYTLF					
	T M	1 -	- (1	0	}
10	AISVGLVLGAFILFAIVGN	[LVILSVANWPALSI	VVIIINTIGGNIL	JIMAVSIYTSLDVM	LCTASILNLLISI	FVLIGS
	FVAFFIPLTIMVITYFLFN	/FFVWIGYVCSSSLG:	INPVIIYTLF (SEÇ	Q ID NO:333)		

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	Т	М	1	-	(1	1)	
	AALAGALLALA	VLATVGGNLL	VIVAIASLD	VMLCTASI	LNLLISLF	VLIGSFVA	FFIPLTIMVI	TYFLFNVFFV	WIGYVO	
	SSSLGINPVII	YTLF (SEQ I	D NO:334)							
	T	М	1	-	(1	2)	
5	TAGDCLIMLIV	LLIVAGNVLV	IVAISLDVM	LCTASILN	LLISLFVL	IGSFVAFF	IPLTIMVITY	FLFNVFFVWI	GYVCSS	
	SLGINPVIIYT	LF(SEQ ID	NO:335)							
	T	м	1	-	(1	3)	
	VVATVVAITIV	SLMTIVGNVL	VMISFSIYT	SLDVMLCT	ASILNLLI	SLFVLIGS	FVAFFIPLTI	MVITYFLFNV	FFVWIG	
	YVCSSSLGINP	VIIYTLF (SE	Q ID NO:3	36)						
10	T	M	1	-	(1	4)	
	MVFIATVRGSL	SLVTVVGNIL	VMLSISIYT	SLDVMLCT	ASILNLLI	SLFVLIGS:	FVAFFIPLTI	MVITYFLFNVI	FFVWIG	
	YVCSSSLGINP	VIIYTLF (SE	Q ID NO:3	37)						
	T	M	1	-	(1	5)	
	WFIAFLTGILA	LVTIIGNILV	IVSFSIYTS	LDVMLCTA:	SILNLLIS	LFVLIGSF	JAFFIPLTIM	VITYFLFNVF	FVWIGY	
15	VCSSSLGINPV:	IIYTLF (SEQ	ID NO:33	8)						
		Non-limi	ting exa	mples o	of longe	er conse	ensus GDR	polypept	ridee	
								= = = = = = = = = = = = = = = = = = = =		
	for domain							any valu	ie or	
	range then	rein, G-p	rotein	recepto	rs are	as foll	Lows:			
	T M	3	-		(1	6	5)	
20	NWPALSIVVIIINTIGGNILVIMAFFACFVLVLTQSSIFSLLAIAINLLISLFVLIGSFVAFFIPLTIMVITYFLFNVFF VWIGYVCSSSLGINPVIIYTLF(SEQ ID NO:339)									
	VWIGYVCSSSL	GINPVIIYTL	F(SEQ ID	NO:339)						
	T M	3	•		(1	6	6)	
	NWPALSIVVIII	INTIGGNILV:	IMAFFACEV	LVLTQSSI	SLLAIAI	FVLIGSFV	AFFIPLTIMV	ITYFLFNVFF	/WIGYV	
	CSSSLGINPVI	(YTLF (SEQ)	ID NO:340)						
25	T M	3	-	•	(1	6	7)	
	NWPALSIVVII:			VLILTQSS:	IALLAIA	VSFVAFFI	PLTIMVITYF	LFNVFFVWIG	rvcsss	
	LGINPVIIYTLE	F(SEQ ID NO	0:341)							
	T M	3	-		(1	6	8)	
	NWPALSIVVIII	INTIGGNILV:	MAVLWLAL	DYVASNASY	LNLLLIS	FFFIPLTI	NITYFLFNVI	FFVWIGYVCS	SLGIN	
30	PVIIYTLF (SEG	Q ID NO:342	2)							
	T M	3	-		(1	6	9)	
	NWPALSIVVII	INTIGGNILV:	(MAVLYVVS	NASVMNLL:	ISSFVAF	FIPLTIMV	TYFLFNVFF	VWIGYVCSSSI	GINPV	
	IIYTLF(SEQ]	ID NO:343)								
	T M	3	-		(1	7	0)	
35	NWPALSIVVIII	INTIGGNILV:	MAVLWIAI	DYVASNASV	/LNLLVIS	FGSFVAFF:	PLTIMVITY	FLFNVFFVWI	SYVCSS	
	SLGINPVIIYTI	LF(SEQ ID 1	NO:344)							
	T M	3	<u>-</u>	•	1	٦	7	1	1	

NWPALSIVVIIINTIGGNILVIMAVCITYLQYLGINASSCSITAFTIIGSFVAFFIPLTIMVITYFLFNVFFVWIGYVCS SSLGINPVIIYTLF(SEQ ID NO:346) - 34 -

T M 3 - (1 7 3)

NWPALSIVVIIINTIGGNILVIMAVFHNFFPIAALFASIYSMTAVAGSFVAFFIPLTIMVITYFLFNVFFVWIGYVCSSS

LGINPVIIYTLF(SEQ ID NO:347)

T M 3 - (1 7 4)

NWPALSIVVIIINTIGGNILVIMAVIASASVSFNLYASVFLLTCLSIGSFVAFFIPLTIMVITYFLFNVFFVWIGYVCSS

SLGINPVIIYTLF(SEQ ID NO:348)

As another non-limiting, illustrative example of a GPR polypeptide consensus sequences across each individual or different transmembrane domains of 5-HT receptors may be made, such as for 5-10 HT, as the following:

5HT consensus(4) KNASALLSVIIINSIGGNVVTAVS (SEQ ID NO:349);

5HT consensus(5) YFLMSLAVTDLVVSFVMPVSAL (SEQ ID NO:350);

5HT consensus(6) AITKIAITWAISGVSVPFIPVWG (SEQ ID NO:351); and

15 5HT consensus(7) LGIIFGTFIIIWLPFFITNLVSPI (SEQ ID NO:352);

Wherein variations and substitutions of amino acids may be made as described herein.

Alternatively, 5-HT consensus sequences may be provided as consensus peptides of the present invention as consensus peptides for individual transmembrane domains, such as 5-HT domains III, V and VII, e.g., as follows:

5-HT consensus (8): IWISLDVLFSTASSIMHLCAISL (SEQ ID NO:353)

5-HT consensus (9): GYTIYSTLVTFYIPSVIMVITYG (SEQ ID NO:354)

5-HT consensus (10): LLNFFNWIGYLNSLINPVIYTLF (SEQ ID NO:355)

This invention is also directed to an antibody which binds an epitope specific for a GPR polypeptide of the present invention and the use of such an antibody to detect the presence of, or measure the quantity or concentration of, the GPR protein in a cell, a cell or tissue extract, a biological fluid, an extract thereof, a solution, or sample, in vitro, in situ, or in vivo.

The term "antibody" is meant to include polyclonal antibodies, monoclonal antibodies (mAbs), chimeric antibodies, anti-idiotypic (anti-Id) antibodies to antibodies specific for GPR polypeptide of the present invention, as well as fragments, consensus polypeptides or chemical derivatives thereof.

Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of animals immunized with an antigen.

A monoclonal antibody contains a substantially homogeneous population of antibodies specific to antigens, which population 10 contains substantially similar epitope binding sites. MAbs may be obtained by methods known to those skilled in the art. See, for example Kohler and Milstein, Nature 256:495-497 (1975); U.S. Patent No. 4,376,110; Ausubel et al, eds., Current Protocols in Molecular Biology, Wiley Interscience, N.Y., (1987, 1992); and Harlow and Lane 15 Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory (1988), the contents of which references are incoporated entirely herein by reference. Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, GILD and any subclass thereof. 20 hybridoma producing a mAb of the present invention may be cultivated in vitro, in situ or in vivo. Production of high titers of mAbs in vivo or in situ makes this the presently preferred method of production.

Chimeric antibodies are molecules different portions of which are derived from different animal species, such as those having variable region derived from a murine mAb and a human immunoglobulin constant region, which are primarily used to reduce immunogenicity in application and to increase yields in production, for example, where murine mAbs have higher yields from hybridomas but higher immunogenicity in humans, such that human/murine chimeric mAbs are used. Chimeric antibodies and methods for their production are known in the art (Cabilly et al, Proc. Natl. Acad. Sci. USA 81:3273-3277 (1984); Morrison et al., Proc. Natl. Acad. Sci. USA 81:6851-6855 (1984); Boulianne et al., Nature 312:643-646 (1984); Cabilly et al.

European Patent Application 171496 (published February 19, 1985);

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Morrison et al., European Patent Application 173494 (published March 5, 1986); Neuberger et al., PCT Application WO 86/01533, (published March 13, 1986); Kudo et al., European Patent Application 184187 (published June 11, 1986); Morrison et al., European Patent Application 173494 (published March 5, 1986); Sahagan et al., J. Immunol. 137:1066-1074 (1986); Robinson et al., International Patent Publication No.PCT/US86/02269 (published 7 May 1987); Liu et al., Proc. Natl. Acad. Sci. USA 84:3439-3443 (1987); Sun et al., Proc. Natl. Acad. Sci. USA 84:214-218 (1987); Better et al., Science 240:1041-1043 (1988); and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory (1988)). These references are incorporated entirely herein by reference.

An anti-idiotypic (anti-Id) antibody is an antibody which recognizes unique determinants generally associated with the antigen15 binding site of an antibody. An Id antibody can be prepared by immunizing an animal of the same species and genetic type (e.g., mouse strain) as the source of the mAb with the mAb to which an anti-Id is being prepared. The immunized animal will recognize and respond to the idiotypic determinants of the immunizing antibody by producing an antibody to these idiotypic determinants (the anti-Id antibody). See, for example, U.S. patent No. 4,699,880, which is herein entirely incorporated by reference.

The anti-Id antibody may also be used as an "immunogen" to induce an immune response in yet another animal, producing a so25 called anti-anti-Id antibody. The anti-anti-Id may be epitopically identical to the original mAb which induced the anti-Id. Thus, by using antibodies to the idiotypic determinants of a mAb, it is possible to identify other clones expressing antibodies of identical specificity.

Accordingly, mAbs generated against a GPR polypeptide of the present invention may be used to induce anti-Id antibodies in suitable animals, such as BALB/c mice. Spleen cells from such immunized mice are used to produce anti-Id hybridomas secreting anti-Id mAbs. Further, the anti-Id mAbs can be coupled to a immunogenic carrier such as keyhole limpet hemocyanin (KLH) or cationized bovine serum albumin and used to immunize additional BALB/c mice. Sera from these mice will contain anti-anti-Id antibodies that have the binding

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properties of the original mAb specific for a GPR polypeptide epitope.

The anti-Id mAbs thus have their own idiotypic epitopes, or "idiotopes" structurally similar to the epitope being evaluated.

The term "antibody" is also meant to include both intact molecules as well as fragments thereof, such as, for example, Fab and F(ab')₂, which are capable of binding antigen. Fab and F(ab'), fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody (Wahl et al., J. Nucl. Med. 24:316-325 (1983)).

It will be appreciated that Fab and F(ab')2 and other fragments of the antibodies useful in the present invention may be used for the detection and quantitation of a GPR polypeptide according to the methods disclosed herein for intact antibody molecules. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab'), fragments).

An antibody is said to be "capable of binding" a molecule 20 if it is capable of specifically reacting with the molecule to thereby bind the molecule to the antibody. The term "epitope" is meant to refer to that portion of any molecule capable of being bound by an antibody which can also be recognized by that antibody. Epitopes or "antigenic determinants" usually consist of chemically 25 active surface groupings of molecules such as amino acids. lipids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics.

An "antigen" is a molecule or a portion of a molecule capable of being bound by an antibody which is additionally capable 30 of inducing an animal to produce antibody capable of binding to an epitope of that antigen. An antigen may have one, or more than one The specific reaction referred to above is meant to indicate that the antigen will react, in a highly selective manner,

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present invention may be used to quantitatively or qualitatively

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detect a GPR polypeptide in a sample or to detect presence of cells which express a GPR polypeptide of the present invention. This can be accomplished by immunofluorescence techniques employing a fluorescently labeled antibody (see below) coupled with light microscopic, flow cytometric, or fluorometric detection.

The antibodies (of fragments thereof) useful in the present invention may be employed histologically, as in immunofluorescence or immunoelectron microscopy, for in situ detection of a GPR polypeptide of the present invention. In situ detection may be accomplished by removing a histological specimen from a patient, and providing the a labeled antibody of the present invention to such a specimen. The antibody (or fragment) is preferably provided by applying or by overlaying the labeled antibody (or fragment) to a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of a GPR polypeptide but also its distribution on the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

Such assays for a GPR polypeptide of the present invention typically comprise incubating a biological sample, such as a biological fluid, a tissue extract, freshly harvested cells such as lymphocytes or leukocytes, or cells which have been incubated in tissue culture, in the presence of a detectably labeled antibody capable of identifying a GPR polypeptide, and detecting the antibody by any of a number of techniques well-known in the art. See, e.g., Harlow and Lane, supra; Ausubel et al, supra; and Sambrook et al, supra.

The biological sample may be treated with a solid phase support or carrier, such as nitrocellulose, or other solid support or carrier which is capable of immobilizing cells, cell particles or soluble proteins. The support or carrier may then be washed with suitable buffers, followed by treatment with a detectably labeled GPR polypeptide-specific antibody. The solid phase support or carrier may then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on said solid support or carrier

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may then be detected by known method steps, see, e.g., Harlow, supra; Ausubel, supra; or Sambrook, supra;

By "solid phase support", "solid phase carrier", "solid support", "solid carrier", "support" or "carrier" is intended any support or carrier capable of binding antigen or antibodies. Wellknown supports or carriers, include glass, polystyrene, polypropylene, polyethylene, dextran, nylon amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. nature of the carrier can be either soluble to some extent or 10 insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or Thus, the support or carrrier configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of 15 a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, polymer test strip, etc. Preferred supports or carriers include polystyrene beads. skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation. 20

The binding activity of a given lot of anti-GPR polypeptide antibody may be determined according to well known method steps. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation. See, e.g., Harlow, supra.

Other such steps as washing, stirring, shaking, filtering and the like may be added to the assays as is customary or necessary for the particular situation.

One of the ways in which a GPR polypeptide-specific antibody, anti-idiotype antibody or fragment thereof, can be detectably labeled is by linking the same to an enzyme and use in an enzyme immunoassay (EIA). This enzyme, in turn, when later exposed to an appropriate substrate, will react with the substrate in such a manner as to produce a chemical modety which can be detected as a second

are not limited to, malate dehydrogenase, staphylococcal nuclease,

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delta-5-steroid isomerase, yeast alcohol dehydrogenase, alphaglycerophosphate dehydrogenase, triose phosphate isomerase,
horseradish peroxidase, alkaline phosphatase, asparaginase, glucose
oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose6- phosphate dehydrogenase, glucoamylase and acetylcholinesterase.
The detection can be accomplished by colorimetric methods which
employ a chromogenic substrate for the enzyme. Detection may also
be accomplished by visual comparison of the extent of enzymatic
reaction of a substrate in comparison with similarly prepared
standards. See, Harlow, supra, Ausubel, supra.

Detection may be accomplished using any of a variety of other immunoassays. For example, by radioactivity labeling the antibodies or antibody fragments, it is possible to detect R-PTPase through the use of a radioimmunoassay (RIA). A good description of RIA maybe found in Laboratory Techniques and Biochemistry in Molecular Biology, by Work et al., North Holland Publishing Company, NY (1978) with particular reference to the chapter entitled "An Introduction to Radioimmune Assay and Related Techniques" by Chard, incorporated entirely by reference herein. The radioactive isotope can be detected by such means as the use of a γ-counter, a scintillation counter or by autoradiography.

It is also possible to label an anti-GPR polypeptide antibody, anti-idiotype antibody or fragment thereof, with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can be then be detected due to fluorescence. Among the most commonly used fluorescent labelling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine, commercially available, e.g., from Molecular Probes, Inc. (Eugene, Ore.).

The antibody can also be detectably labeled using fluorescence emitting metals such as ¹⁵²EU, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriamine pentaacetic acid (EDTA).

The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the

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chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

An antibody molecule of the present invention may be adapted for utilization in a immunometric assay, also known as a "two-site" or "sandwich" assay. In a typical immunometric assay, a quantity of unlabeled antibody (or fragment of antibody) is bound to a solid support or carrier and a quantity of detectably labeled soluble antibody is added to permit detection and/or quantitation of the ternary complex formed between solid-phase antibody, antigen, and labeled antibody.

Typical, and preferred, immunometric assays include "forward" assays in which the antibody bound to the solid phase is first contacted with the sample being tested to extract the antigen form the sample by formation of a binary solid phase antibody-antigen complex. After a suitable incubation period, the solid support or carrier is washed to remove the residue of the fluid sample, including unreacted antigen, if any, and then contacted with the solution containing an unknown quantity of labeled antibody (which functions as a "reporter molecule"). After a second incubation period to permit the labeled antibody to complex with the antigen bound to the solid support or carrier through the unlabeled antibody, the solid support or carrier is washed a second time to remove the unreacted labeled antibody.

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[&]quot;reverse" assays are used. A simultaneous assay involves a single

incubation step as the antibody bound to the solid support or carrier and labeled antibody are both added to the sample being tested at the same time. After the incubation is completed, the solid support or carrier is washed to remove the residue of fluid sample and uncomplexed labeled antibody. The presence of labeled antibody associated with the solid support or carrier is then determined as it would be in a conventional "forward" sandwich assay.

In the "reverse" assay, stepwise addition first of a solution of labeled antibody to the fluid sample followed by the addition of unlabeled antibody bound to a solid support or carrier after a suitable incubation period is utilized. After a second incubation, the solid phase is washed in conventional fashion to free it of the residue of the sample being tested and the solution of unreacted labeled antibody. The determination of labeled antibody associated with a solid support or carrier is then determined as in the "simultaneous" and "forward" assays. See, e.g., for the abovementioned immunological techniques, Harlow, supra; Ausubel et al, supra; and Sambrook et al, supra. GPR polypeptides of the present invention can be made by chemical synthesis or by recombinant methods, wherein chemical synthesis is preferred.

Synthetic production of transmembrane proteins of the present invention

GPR polypeptides, variants and chemical derivatives thereof can be synthesized according to known method steps, including portions of known GPR transmembrane domains, consensus peptides thereof, conservative substitution derivative thereof or functional derivatives thereof.

Chemical polypeptide synthesis is a rapidly evolving area in the art, and methods of solid phase polypeptide synthesis are well-described in the following references, hereby entirely incorporated by reference: (Merrifield, B., J. Amer. Chem. Soc. 85:2149-2154 (1963); Merrifield, B., Science 232:341-347 (1986); Wade, J.D. et al., Biopolymers 25:S21-S37 (1986); Fields, G.B., Int. J. Polypeptide Prot. Res. 35:161 (1990); MilliGen Report Nos. 2 and 2a, Millipore Corporation, Bedford, MA, 1987) Ausubel et al, supra, and Sambrook et al. supra.

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In general, as is known in the art, such methods involve blocking or protecting reactive functional groups, such as free amino, carboxyl and thio groups. After polypeptide bond formation, the protective groups are removed (or de-protected). 5 addition of each amino acid residue requires several reaction steps for protecting and deprotecting. Current methods utilize solid phase synthesis, wherein the C-terminal amino acid is covalently linked to an insoluble resin particle large enough to be separated from the fluid phase by filtration. Thus, reactants are removed by washing the resin particles with appropriate solvents using an automated programmed machine The completed polypeptide chain is cleaved from the resin by a reaction which does not affect polypeptide bonds.

In the more classical method, known as the "tBoc method," the amino group of the amino acid being added to the resin-bound C-terminal amino acid is blocked with tert-butyloxycarbonyl chloride (tBoc). This protected amino acid is reacted with the bound amino in the presence of the condensing dicyclohexylcarbodiimide, allowing its carboxyl group to form a polypeptide bond the free amino group of the bound amino acid. amino-blocking group is then removed by acidification trifluoroacetic acid (TFA); it subsequently decomposes into gaseous carbon dioxide and isobutylene. These steps are repeated cyclically for each additional amino acid residue. A more vigorous treatment with hydrogen fluoride (HF) or trifluoromethanesulfonyl derivatives is common at the end of the synthesis to cleave the benzyl-derived side chain protecting groups and the polypeptide-resin bond.

More recently, the preferred "Fmoc" technique has been introduced as an alternative synthetic approach, offering milder reaction conditions, simpler activation procedures and compatibility 30 with continuous flow techniques. This method was used, e.g., to prepare the peptide sequences disclosed in the present application. the lpha-amino group is protected by the base 9-fluorenylmethoxycarbonyl (Fmoc) group. The benzyl side chain protecting groups are replaced by the more acta askets

or are albeitelik . Himethy, Formamide .DMF;, and the final HF cleavage treatment is eliminated. A TFA

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solution is used instead to cleave side chain protecting groups and the polypeptide resin linkage simultaneously.

At least three different polypeptide-resin linkage agents can be used: substituted benzyl alcohol derivatives that can be cleaved with 95% TFA to produce a polypeptide acid, methanolic ammonia to produce a polypeptide amide, or 1% TFA to produce a protected polypeptide which can then be used in fragment condensation procedures, as described by Atherton, E. et al., J. Chem. Soc. Perkin Trans. 1:538-546 (1981) and Sheppard, R.C. et al., Int. J. 10 Polypeptide Prot. Res. 20:451-454 (1982). Furthermore, highly reactive Fmoc amino acids are available as pentafluorophenyl esters or dihydro-oxobenzotriazine esters derivatives, saving the step of activation used in the tBoc method.

Sequences available to use as a basis for polypeptide 15 synthesis can be based on published sequences of G-protein coupled receptors, ligands and/or effectors, wherein the transmembrane or functional domains correspond to sections of hydrophobic or other amino acids of 5 to 100 amino acids, such as 5-10, 10-15, 15-25, 20-25, 23-27, 25-30, 28-35, 20-40, 10-40, 20-30, 30-40, 40-50, 10-80, 20 20-60 or 25-40 amino acids in length. Recombinant production of GPR polypeptides can be accomplished according to known method steps. Standard reference works setting forth the general principles of recombinant DNA technology include Watson, J.D. et al., Molecular Biology of the Gene, Volumes I and II, The Benjamin/Cummings 25 Publishing Company, Inc., publisher, Menlo Park, CA (1987); Darnell, J.E. et al., Molecular Cell Biology, Scientific American Books, Inc., publisher, New York, NY (1986); Lewin, B.M., Genes III, John Wiley & Sons, publishers, New York, NY (1989); Old, R.W., et al., Principles of Gene Manipulation: An Introduction to Genetic 30 Engineering, 2d edition, University of California Press, publisher, Berkeley, CA (1981); Ausubel et al, eds., Current Protocols in Molecular Biology, Wiley Interscience, publisher, New York, NY (1987, 1992); and Sambrook et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory, publisher, Cold 35 Spring Harbor, NY (1989), the entire contents of which references are herein incorporated by reference.

A nucleic acid sequence encoding a GPR polypeptide of the present invention may be recombined with vector DNA in accordance with conventional techniques, including blunt-ended or staggered-ended termini for ligation, restriction enzyme digestion to provide appropriate termini, filling in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and ligation with appropriate ligases. Techniques for such manipulations are disclosed, e.g., by Ausubel et al, supra, and are well known in the art.

10 A nucleic acid molecule, such as DNA, is said to be "capable of expressing" a polypeptide if it contains nucleotide sequences which contain transcriptional and translational regulatory information and such sequences are "operably linked" to nucleotide sequences which encode the polypeptide. An operable linkage is a linkage in which the regulatory DNA sequences and the DNA sequence sought to be expressed are connected in such a way as to permit gene expression as GPR polypeptides in recoverable amounts. The precise nature of the regulatory regions needed for gene expression may vary from organism to organism, as is well known in the analogous art. See, e.g., Sambrook, supra and Ausubel supra.

The present invention accordingly encompasses the expression of a GPR polypeptide, in either prokaryotic or eukaryotic cells, although eukaryotic expression is preferred.

Preferred hosts are bacterial or eukaryotic hosts including bacteria, yeast, insects, fungi, bird and mammalian cells either in vivo, or in situ, or host cells of mammalian, insect, bird or yeast origin. It is preferred that the mammalian cell or tissue is of human, primate, hamster, rabbit, rodent, cow, pig, sheep, horse, goat, dog or cat origin, but any other mammalian cell may be used.

Further, by use of, for example, the yeast ubiquitin hydrolase system, in vivo synthesis of ubiquitin-transmembrane polypeptide fusion proteins may be accomplished. The fusion proteins so produced may be processed in vivo or purified and processed in

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methionine residues in direct yeast (or bacterial) expression may be

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avoided. Sabin et al., *Bio/Technol.* 7(7): 705-709 (1989); Miller et al., *Bio/Technol.* 7(7): 698-704 (1989).

Any of a series of yeast gene expression systems incorporating promoter and termination elements from the actively expressed genes coding for glycolytic enzymes produced in large quantities when yeast are grown in mediums rich in glucose can be utilized to obtain GPR polypeptides of the present invention. Known glycolytic genes can also provide very efficient transcriptional control signals. For example, the promoter and terminator signals of the phosphoglycerate kinase gene can be utilized.

Production of GPR polypeptides or functional derivatives thereof in insects can be achieved, for example, by infecting the insect host with a baculovirus engineered to express transmembrane polypeptide by methods known to those of skill. See Ausubel et al, eds. Current Protocols in Molecular Biology, Wiley Interscience, §§16.8-16.11 (1987, 1992).

In a preferred embodiment, the introduced nucleotide sequence will be incorporated into a plasmid or viral vector capable of autonomous replication in the recipient host. Any of a wide variety of vectors may be employed for this purpose. See, e.g., Ausubel et al, supra, s, <a href=

Preferred prokaryotic vectors known in the art include

30 plasmids such as those capable of replication in <u>E. coli</u> (such as, for example, pBR322, ColE1, pSC101, pACYC 184, \piVX). Such plasmids are, for example, disclosed by Maniatis, T., et al. (Molecular Cloning, A Laboratory Manual, Second Edition, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989); Ausubel et al, eds., Current

35 Protocols in Molecular Biology, Wiley Interscience, New York, NY (1987, 1992)). Bacillus plasmids include pC194, pC221, pT127, etc. Such plasmids are disclosed by Gryczan, T. (In: The Molecular

Biology of the Bacilli, Academic Press, NY (1982), pp. 307-329). Suitable Streptomyces plasmids include pIJ101 (Kendall, K.J., et al., J. Bacteriol. 169:4177-4183 (1987)), and streptomyces bacteriophages such as ϕ C31 (Chater, K.F., et al., In: Sixth International Symposium on Actinomycetales Biology, Akademiai Kaido, Budapest, Hungary (1986), pp. 45-54). Pseudomonas plasmids are reviewed by John, J.F., et al. (Rev. Infect. Dis. 8:693-704 (1986)), and Izaki, K. (Jpn. J. Bacteriol. 33:729-742 (1978); and Ausubel et al, supra).

The expressed protein may be isolated and purified in accordance with conventional conditions, 10 such as extraction, precipitation, chromatography, affinity chromatography, electrophoresis, or the like. For example, the cells may be collected by centrifugation, or with suitable buffers, lysed, and the protein isolated by column chromatography, for example, DEAE-cellulose, phosphocellulose, polyribocytidylic acid-agarose, 15 hydroxyapatite or by electrophoresis or immunoprecipitation. Alternatively, the transmembrane polypeptide or functional derivative thereof may be isolated by the use of anti-transmemorane polypeptide antibodies. Such antibodies may be obtained by well-known methods, 20 some of which are mentioned below. These antibodies may be immobilized on cellulose, agarose, hollow fibers, or cellulose filters by covalent chemical derivatives by methods well known to those skilled in the art.

As discussed herein, GPR polypeptides of the present invention may be further modified for purposes of drug design, such as for example to reduce immunogenicity, to prevent solubility and/or enhance delivery, or to prevent clearance or degradation.

Appropriate modification of the primary amino acid sequence of GPR polypeptides of the present invention, obtained by mutagenesis or utilizing fragments of other related forms of G-protein transmembrane proteins, as described herein, will allow the creation of molecules which bind G-protein coupled receptors with higher affinity than that exhibited by naturally occurring transmembrane

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advantages over larger polypeptides. These advantages include (1) greater stability and diffusibility, and (2) less immunogenicity.

Since polypeptides according to the present invention are generally small (10-40, 20-30, 15-25, 30-45 amino acids), cell or 5 tissue sources of G-protein coupled receptors are not required to . practice the present invention, since known polypeptide syntheses steps can be used without undue experimentation to provide GPR polypeptides or sequences substantially corresponding thereto. Pharmaceutical Preparations

10 Preparations of GPR polypeptides for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions, which may contain auxiliary agents or excipients which are known in the art. Pharmaceutical compositions such as tablets and capsules can also be prepared according to 15 routine methods.

By the term "protection" from infection or disease as used herein is intended "prevention," "suppression" or "treatment." "Prevention" involves administration of a GPR polypeptide, polypeptide derivative, or anti-idiotypic antibody prior to the 20 <u>induction</u> of the disease.

"Suppression" involves administration of the composition prior to the clinical appearance of the disease.

"Treatment" involves administration of the protective composition <u>after the appearance</u> of the disease. It will be 25 understood that in human and veterinary medicine, it is not always possible to distinguish between "preventing" and "suppressing" since the ultimate inductive event or events may be unknown, latent, or the patient is not ascertained until well after the occurrence of the event or events. Therefore, it is common to use the term "prophylaxis" as distinct from "treatment" to encompass both . "preventing" and "suppressing" as defined herein. The "protection," as used herein, is meant to include "prophylaxis."

At least one GPR polypeptide, antibody or anti-idiotypic antibody of the present invention may be administered by any means 35 that achieve their intended purpose, for example, to treat GPR related pathologies, such as psychotic disorders, schizophrenia, by inhibition of binding of Dopamine D. receptors

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using a GPR polypeptide corresponding to a fragment or consensus portion of a dopamine D_2 transmembrane domain; in the form of a pharmaceutical composition.

For example, administration of such a composition may be by various parenteral routes such as subcutaneous, intravenous, intradermal, intramuscular, intraperitoneal, intranasal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. Parenteral administration can be by bolus injection or by gradual perfusion over time.

A preferred mode of using a GPR pharmaceutical composition of the present invention is by intravenous or parenteral application.

A typical regimen for preventing, suppressing, or treating G-protein coupled receptor pathologies, such as dopamine receptor related schizophrenia, comprises administration of an effective amount of a GPR polypeptide, consensus sequence, or chemical derivative thereof, administered over a period of one or several days, up to and including between one week and about 24 months.

It is understood that the dosage of a GPR polypeptide of the present invention administered in vivo or in vitro will be dependent upon the age, sex, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. The ranges of effective doses provided below are not intended to limit the inventors and represent preferred dose ranges. However, the most preferred dosage will be tailored to the individual subject, as is understood and determinable by one of skill in the art, without undue experimentation.

The total dose required for each treatment may be administered by multiple doses or in a single dose. a GPR polypeptide or functional a chemical derivative thereof may be administered alone or in conjunction with other therapeutics directed to GPR related pathologies, such as a the dopamine receptor related pathology as a non limiting example, or directed to other symptoms of the disease.

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body weight, and preferably from about 10 μg to about 50 mg/kg body

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weight, such 0.05, 0.07, 0.09, 0.1, 0.5, 0.7, 0.9, 1, 2, 5, 10, 20, 25, 30, 40, 45, or 50 mg/kg.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions, which may contain auxiliary agents or excipients which are known in the art. Pharmaceutical compositions such as tablets and capsules can also be prepared according to routine methods.

Pharmaceutical compositions comprising at least one GPR polypeptide of the present invention may

include all compositions wherein the GPR polypeptide is contained in an amount effective to achieve its intended purpose. In addition to the GPR polypeptide, a pharmaceutical composition may contain suitable pharmaceutically acceptable carriers, such as comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically.

Pharmaceutical compositions include suitable solutions for administration intravenously, subcutaneously, dermally, orally, mucosally, rectally or may by injection or orally, and contain from about 0.01 to 99 percent, preferably from about 20 to 75 percent of active component (i.e. the antibody) together with the excipient. Pharmaceutical compositions for oral administration include tablets and capsules. Compositions which can be administered rectally include suppositories.

Example 1: Synthesis of a G-Protein Transmembrane Polypeptide and Consensus Polypeptide

The polypeptides in Figs. 1-5 were synthesized using the following procedure and include the following characteristics.

Peptide I (SEQ ID NO:1), as shown in Fig. 1, was used as a control for hydrophobic interaction alone as the mechanism of binding and was run in parallel with the test polypeptides described below. Polypeptide II (SEQ ID NO:2), as shown in Fig. 2, represents a membrane-spanning fragment of transmembrane segment III in the dopamine D_2 receptor. This particular fragment was chosen since it has been implicated in the β -adrenergic receptor as having many residues which are involved in ligand binding interaction.

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Polypeptide III (SEQ ID NO:3), as shown in Fig. 3, represents the consensus polypeptide which was developed as a model for the dopamine D_2 system and polypeptide IV (SEQ ID NO:4), as shown in Fig. 4, a control for length dependence to show how critical the polypeptide 5 length is in binding studies. Polypeptide V (SEQ ID NO:5), as shown in Fig. 5, is a consensus sequence of transmembrane domains of dopamine receptors D, and D.

The above polypeptides I-V (SEQ ID NOS:1-5), as shown in Figs. 1-5, respectively, were synthesized using solid phase synthesis 10 on a Milligen 9600 polypeptide synthesizer using Fmoc amino acids (provided by Milligen/Biosearch) and PALpolystyrene (Milligen/Biosearch). Coupling times were 1 hour the polypeptides were cleaved bу trifluoroacetic acid/phenol/H₂O/thioanisole/ethanedithiol (82.5:5:5:5:5) at room temperature for 2 hours. The filtrate was collected and washed with 2 mL of trifluoroacetic acid (TFA) and 1 mL of dichloromethane (DCM). The filtrate was reduced in vacuo to 2 ml in volume and the resulting polypeptide was precipitated out by the addition of water. polypeptides were then dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) Eastman]; lyophilized; and stored at purification. Polypeptides I-V (SEQ ID NOS:1-5), were purified using reverse-phase HPLC using a preparative Vydac C4 column (Vydac) at 60°C at a flow rate of 6.0 mL/min with a linear gradient of 0-100% B in a 60 min period at a UV detection wavelength of 275 nm.

25 Due to the highly hydrophobic nature of these polypeptides, methanol was used with 0.1% (W/V) TFA and 0.5% (W/V) HFIP as solvent A and 2-propanol with 0.1% TFA as solvent B, in order to purify these polypeptides. Further purification was performed with an analytical C4 column (Vydac) with an isocratic gradient of 40% B at a flow rate 30 of 1 ml/min. Identity of the polypeptides was confirmed by Fast-atom bombardment mass spectrometry and electrospray mass spectrometry and amino acid analysis. Stock solutions of polypeptides were made in HFIP and stored at -20°- 80°C.

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The figure of the state of the calibrated using 1 0.1% (w/v) solution of d (+)-camphorsulfonic acid

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(Aldrich) and the wavelength of the CD signal was set using standard absorbance peaks of benzene vapor. Polypeptide concentrations were determined in a Cary 210 UV spectrophotomer with the absorbance measured at 280 nm. Helical content was estimated using CD signal intensity according to the method of Chen. et al Biochem. 13:3350-3359 (1974). This calculation compares the experimental ellipticity at 222 nm ([0]222) ([0]) to a theoretical [0]222. The theoretical [0]222 is empirically adjusted to account for differences in polypeptide length and is based on experimental CD data from a series of proteins with known crystal structures. Since both the curve shape and magnitude are important in analysis of a CD spectrum for secondary structure contributions, we also considered qualitatively the contributions to the spectral shapes from different secondary structures using reference curves for poly (L-lysine).

Fig. 6 shows a CD spectrum of the consensus polypeptide III (SEQ ID NO:3) demonstrating that the polypeptide III is only partially helical in a solvent system in which most membrane polypeptides are strongly helical.

Preparation of Small Unilamellar Vesicles. Polypeptides
were incorporated into DMPC vesicles at lipid:peptide ratio of 147:1
in the following manner: polypeptide in HFIP was mixed with
dimyrystyroyl- phosphatidylcholine (synthetic) (DMPC) in dry
chloroform and dried to a film with a stream of dry nitrogen at 0°C.
This residue was then dried further overnight under a vacuum (1 x 10°2
torr). The residue was then hydrated in 100 mM NaCl and sonicated
for a 30-min period under nitrogen at 0°C. The suspension was
sedimented for a 30-min at 100,000 g (4°C) to remove any residual
titanium particles and large unilamellar vesicles. The supernatant
was removed and sedimented once more at 159,000 g for a 45 min period
at 4°C. The supernatant in the lower portion was used immediately.
This basic procedure has been shown to reliably produce small
unilamellar vesicles.

Radioligand Binding Assays. A 0.50 mL volume of 1.00 nM [3H]-spiperone (New England specific activity 21.4 Ci/mmol) was added to assay tubes which contained 0.5 mL lipid/peptide supernatant, 0.5 mL Tris buffer pH 7.4 and 0.5 mL of cold drug for a final volume of 2.0 mL. Nonspecific binding was defined in the presence of 1 uM of

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Bright Could be 64 for each

(+) butaclamol or 1 uM spiperone. Appropriate controls for lipid vesicles containing no polypeptide were also run. Assay tubes were prepared in triplicate and the mixture was incubated for 1 h at 25°C. Incubation was terminated by filtration through filters presoaked in 0.1% polyethyleneimine (w/v, Sigma) for at least 1 h prior to use.

Filters were then washed with 6.0 mL of cold 50 mM Tris-HCl buffer, pH 7.40. For detection of radioactivity, filters were placed in 2.0 mL of scintillation fluid (Scintiverse) and incubated for 24 h. The activity of the tritium was determined in a Beckman LS 7500 liquid scintillation counter. Specific binding of [3H]-spiperone was defined as the difference in binding in the presence and absence of unlabeled (+) butaclamol.

Fig. 7 shows results of radioligand binding assays comparing polypeptide I (SEQ ID NO:1) as a control unit polypeptide III (SEQ ID NO:3) according to the present invention. Polypeptide III (SEQ ID NO:3) is shown to unexpectedly provide receptor-like functional binding, as demonstrated by binding to the neuroleptic agent, spiperone, into a stereoselective, concentration-dependent manner.

It has also been demonstrated that as little as 0.1% of a GPR polypeptide according to the present invention is able to form a receptor-like functional binding site. Thus, a GPR polypeptide of the present invention is unexpectedly shown to act both as GPR ligands and GPR binding sites.

All references cited herein, including journal articles or abstracts, published or corresponding U.S. or foreign patent applications, issued U.S. or foreign patents, or any other references, are entirely incorporated by reference herein, including all data, tables, figures, and text presented in the cited references. Additionally, the contents of the references cited within the references cited herein are also entirely incorporated by reference.

Reference to known method steps, conventional methods

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The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art (including the contents of the references cited herein), readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the generic concept of the present invention. Therefore, such adaptations and modifications are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance presented herein.

- 55 -

SEQUENCE LISTING

```
(1) GENERAL INFORMATION:
          (i) APPLICANT: Murphy, Randall B.
                         Schuster, David I.
 5
         (ii) TITLE OF INVENTION: POLYPEPTIDES OF G-COUPLED RECEPTOR PROTEINS, AND
     COMPOSITIONS AND METHODS THEREOF
        (iii) NUMBER OF SEQUENCES: 95
         (iv) CORRESPONDENCE ADDRESS:
               (A) ADDRESSEE: BROWDY AND NEIMARK
10
               (B) STREET: 419 Seventh Street, N.W.
               (C) CITY: Washington
               (D) STATE: D.C.
(E) COUNTRY: USA
               (F) ZIP: 20004
15
          (v) COMPUTER READABLE FORM:
               (A) MEDIUM TYPE: Floppy disk
               (B) COMPUTER: IBM PC compatible
               (C) OPERATING SYSTEM: PC-DOS/MS-DOS(D) SOFTWARE: PatentIn Release #1.0, Version #1.25
20
         (vi) CURRENT APPLICATION DATA:
               (A) APPLICATION NUMBER: US 07/943,236
               (B) FILING DATE: 10-SEP-1992
               (C) CLASSIFICATION:
       (viii) ATTORNEY/AGENT INFORMATION:
25
               (A) NAME: Townsend, Kevin G.
               (B) REGISTRATION NUMBER: 34,033
               (C) REFERENCE/DOCKET NUMBER: MURPHY=2
         (ix) TELECOMMUNICATION INFORMATION:
               (A) TELEPHONE: 202-628-5197
30
               (B) TELEFAX: 202-737-3528
               (C) TELEX: 248633
     (2) INFORMATION FOR SEQ ID NO:1:
          (i) SEQUENCE CHARACTERISTICS:
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               (B) TYPE: amino acid
               (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
         (x1) SEQUENCE DESCRIPTION: SEQ ID NO:1:
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               (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
50
         (ii) MOLECULE TYPE: peptide
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Led Ash Led Ser Ara Tie Ser Led Lys Lys Lys 20 25

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- 56 -

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               (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
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               (B) TYPE: amino acid
               (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
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               (B) TYPE: amino acid
               (C) STRANDEDNESS: single
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         (ii) MOLECULE TYPE: peptide
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               (B) TYPE: amino acid(C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
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          (ii) MOLECULE TYPE: peptide
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           Phe Pro Cys Tyr Leu Tyr Ala Ile Val Ile Thr Tyr Gly Ser Phe Ala
```

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										- 5	, -						
		Cys	Trp	Leu	Trp	Thr 85	Leu	Ile	Cys	Leu	Ala 90	Ile	Ser	Ile	Tyr	Met 95	Leu
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		Val	Asn 210	Arg	Ile	Val	Asn	Gly 215	Leu	Asn	Trp	Pro	Pro 220	Ala	Leu	Asn	Ile
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					260		Phe			265					270		
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		Lys	Thr 290	Met	Leu	Gly	His	Pro 295	Thr	Gly	Asp	Asp	Val 300	Gln	Cys	Ser	Ser
30		Asp 305	Leu	Gln	Cys	Ser	Leu 310	Glu	Arg	His	Pro	Asn 315	Met	Val			
35	(2)	(i)	SEQ (A (B	UENC) LE) TY	E CH NGTH PE:	ARAC : 34 amin	ID No TERI 9 am 0 ac SS:	STIC ino id	acid	6							
ر د		(ii)	(D) TO	POLO	GY:	line pept	ar	16								
40		(xi) Val 1	S EQ Tyr	UENC Ile	E DE Thr	SCRI Val 5	PTIO Glu	N: S Leu	EQ I Ala	D NO Ile	1:7: Ala 10	Val	Leu	Ala	Thr	Leu 15	Gly
		Asn	Val	Leu	Val 20	Cys	Trp	Ala	Val	Trp 25	Leu	Asn	Ser	Asn	. Leu 30	Asn	. Val
e C		- ä.	11e 50	: A.d	ile	F1C	ène	Ата 55	**E	îni	2 2 %	261	Tr.1 60	ولدك	rile	: <u>`</u> y" w	n_a

Ala Cys His Asn Cys Leu Phe Phe Ala Cys Phe Val Leu Val Leu Thr

Physical Company

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	65					70					75					80
	Gln	Ser	Ser	Ile	Phe 85	Ser	Leu	Leu	Ala	Ile 90	Ala	Ile	Asp	Arg	Tyr 95	Ile
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	Ala	Lys	Gly 115	Ile	Ile	Ala	Val	Cys 120	Trp	Val	Leu	Ser	Phe 125	Ala	Ile	Gly
	Leu	Thr 130	Pro	Met	Leu	Gly	Trp 135	Asn	Asn	Cys	Ser	Gln 140	Pro	Lys	Glu	Gly
10	Arg 145	Asn	Tyr	Ser	Gln	Gly 150	Cys	Gly	Glu	Gly	Gln 155	Val	Ala	Cys	Leu	Phe 160
	Glu	Asp	Val	Val	Pro 165	Met	Asn	Tyr	Met	Val 170	Tyr	Tyr	Asn	Phe	Phe 175	Ala
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		Ala 210					215	-				220				
20	225	Ile				230					235					240
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		Ile 290					295					300				
30	305	Thr				310					315					320
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35	Ser	Ala	Pro	His 340	Pro	Glu	Arg	Arg	Pro 345	Asn	Gly	Tyr	Thr			
40		SEQI (A (B (C (D	UENCI) LEI) TYI) STI) TOI	E CHI NGTH PE: (RAND) POLO(ARAC' : 314 amin EDNE: GY:	TERI: 4 am: 5 ac: SS: 1 ine	STIC: ino id sing: ar	acid	s							
		MOL:			•	•		EQ I	D NO	:8:						
45		Tyr									Leu	Val	Ser	Val	Pro 15	Gly
	Trp	Leu	Val	Ile 20	Trp	Ala	Val	Lys	Val 25	Asn	Gln	Ala	Leu	Arg 30	Asp	Ala

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		Thr	Phe	Cys 35	Phe	Ile	Val	Ser	Ile 40	Ala	Val	Ala	Asp	Val 45	Ala	Val	Gly
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5		Tyr 65	Phe	His	Thr	Cys	Leu 70	Met	Val	Ala	Cys	Pro 75	Val	Leu	Ile	Leu	Thr 80
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		Ala	Ala	Val 115	Ala	Ile	Ala	Gly	Cys 120	Trp	Ile	Leu	Ser	Phe 125	Val	Val	Gly
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35		Glu 305	Asp	Pro	Pro		Glu 310	Ala	Pro	His	Asp						
	121	TNICO		TON	EOD.	CEO	TTO NO	0.0.									

(2) INFORMATION FOR SEQ ID NO:9:

40

PARTER DESIGNATION

- (i) SEQUENCE CHARACTERISTICS:

 - (A) LENGTH: 342 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single

S.OBACA CACADA 12. Ala The C.S.Oly T.- The Tax A., 1919 -5 10

Thr Gly Asn Leu Leu Val Leu Ile Ser Phe Lys Val Asn Thr Glu Leu

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					20					25					30		
		Lys	Thr	Val 35	Asn	Asn	Tyr	Phe	Leu 40	Leu	Ser	Ile	Ala	Cys 45	Ala	Asp	Leu
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		Gly 65	Thr	Leu	Ala	Cys	Asp 70	Leu	Trp	Leu	Ala	Leu 75	Asp	Tyr	Val	Ala	Ser 80
		Asn	Ala	Ser	Val	Leu 85	Asn	Leu	Leu	Leu	Ile 90	Ser	Phe	Asp	Arg	Tyr 95	Phe
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35		Leu	Ile 290	Cys	Tyr	Val	Asn	Ser 295	Thr	Ile	Asn	Pro	Trp 300	Tyr	Ala	Leu	Cys
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40		Thr	Pro	Ser	Arg 340	Gln	Cys										
	(2)	TNEO	יייי מאברו	TON	EOD :	033	א כד	0.10	_								

- (2) INFORMATION FOR SEQ ID NO:10:
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 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
- 45

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	(ii)	(D MOL) TO ECUL	POLO E TY	GY: PE:	line pept	ar ide									
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	Ile	Gly	Asn	Ile 20	Leu	Val	Met	Val	Ser 25	Ile	Lys	Val	Asn	Arg 30	His	Туз
	Phe	Leu	Phe 35	Ser	Ile	Ala	Cys	Ala 40	qaA	Leu	Ile	Ile	Gly 45	Val	Phe	Sei
10	Met	Asn 50	Leu	Tyr	Thr	Leu	Tyr 55	Thr	Val	Ile	Gly	Tyr 60	Trp	Pro	Leu	Gly
	Pro 65	Val	Val	Cys	Asp	Leu 70	Tyr	Val	Val	Ser	Asn 75	Ala	Ser	Val	Met	Asr 80
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	Thr	Tyr	Pro	Val 100	Lys	Arg	Thr	Thr	Lys 105	Met	Ala	Gly	Met	Mct 110	Ile	Ala
	Ala	Ala	Trp 115	Val	Leu	Ser	Phe	Ile 120	Leu	Trp	Ala	Pro	Ala 125	Ile	Leu	Ph∈
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25	Ala	Phe	Tyr	Leu	Pro 165	Val	Ile	Ile	Met	Ile 170	Val	Leu	Tyr	Trp	His 175	Ile
	Ser	Arg	Ala	Ser 180	I.ys	Ser	Arg	Ile	Lys 185	Lys	Asp	Lys	Lys	Glu 190	Pro	Val
	Ala	Asn	Gln 195	Asp	Pro	Val	Ser	Pro 200	Ser	Leu	Val	Gln	Gly 205	Arg	Ile	Val
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35	Ile	Ala	Ile	Leu	Leu 245	Ala	Phe	Ile	Ile	Thr 250	Trp	Ala	Pro	Tyr	Asn 255	Val
	Met	Val	Leu	Ile 260	Asn	Thr	Phe	Cys	Ala 265	Pro	Cys	Ile	Pro	Asn 270	Thr	Val
	Trp	Arg	Ile 275	Gly	Tyr	Trp	Leu	Cys 280	Tyr	Ile	Asn	Ser	Thr 285	Ile	Asn	Pro
40	Ala	Cys 290	Tyr	Ala	Leu	Cys	Asn 295	Ala	Thr	Phe	Lys	Lys	Thr	Phe	Lys	His

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	(ii)	(C)	TOI	RANDI POLOC	EDNES	SS: s linea	sing] ar	Le								
5	(xi) Trp 1										Ala	Leu	Val	Thr	Ile 15	Ile
	Gly	Asn	Ile	Leu 20	Val	Ile	Val	Ser	Phe 25	Lys	Val	Asn	Lys	Gln 30	Leu	Lys
10	Thr	Val	Asn 35	Asn	Tyr	Phe	Leu	Leu 40	Ser	Leu	Ala	Cys	Ala 45	qaA	Leu	Ile
	Ile	Gly 50	Val	Ile	Ser	Met	Asn 55	Leu	Phe	Thr	Thr	Tyr 60	Ile	Ile	Met	Asn
15	Arg 65	Trp	Ala	Leu	Gly	Asn 70	Thr	Ala	Сув	qaA	Leu 75	Trp	Ile	ala	Ile	As p 80
	Tyr	Val	Ala	Ser	Asn 85	Ala	Ser	Val	Leu	Asn 90	Leu	Leu	Val	Ile	Ser 95	Phe
	Asp	Arg	Tyr	Phe 100	Ser	Ile	Thr	Arg	Pro 105	Leu	Thr	Tyr	Arg	Ala 110	Lys	Arg
20	Thr	Thr	Lys 115	Arg	Ala	Gly	Val	Met 120	Ile	Gly	Leu	Ala	Trp 125	Vai	Ile	Ser
	Phe	Val 130	Leu	Trp	Ala	Pro	Ala 135	Ile	Leu	Phe	Trp	Gln 140	Tyr	Phe	Val	Gly
25	Lys 145	Arg	Thr	Val	Pro	Pro 150	Gly	Glu	Cys	Phe	Ile 155	Gln	Phe	Leu	Ser	Glu 160
	Pro	Thr	Ile	Thr	Phe 165	Gly	Thr	Ala	Ile	Ala 170	Ala	Phe	Tyr	Met	Pro 175	Val
	Thr	Ile	Met	Arg 180	Ile	Leu	Tyr	Trp	Arg 185	Ile	Tyr	Lys	Glu	Thr 190	Glu	Lys
30	Arg	Thr	Lys 195	Glu	Leu	Ala	Gly	Leu 200	Gln	Ala	Ser	Gly	Thr 205	Glu	Ala	Glu
	Thr	Glu 210	Asn	Phe	Val	His	Pro 215	Thr	Gly	Ser	Ser	Arg 220	Ser	Cys	Ser	Ser
35	Tyr 225	Glu	Leu	Gln	Gln	Gln 230	Lys	Arg	Phe	Ala	Leu 235	Lys	Thr	Arg	Ser	Gln 240
	Ile	Thr	Lys	Arg	Lys 245	Leu	Leu	Val	Lys	Glu 250	Lys	Lys	Ala	Ala	Gln 255	Thr
	Leu	Ser	Ala	Ile 260	Leu	Leu	Ala	Phe	Ile 265	Ile	Thr	Trp	Thr	Pro 270	Tyr	Asn
40	Ile	Met	Val 275	Leu	Val	Asn	Thr	Phe 280	Cys	Asp	Ser	Сув	Ile 285	Pro	Lys	Thr
	Tyr	Trp 290	Asn	Leu	Gly	Gly	Tyr 295	Trp	Leu	Cys	Tyr	Ile 300	Asn	Ser	Thr	Val
45	Asn 305	Pro	Val	Cys	Tyr	Ala 310	Leu	Cys	Asn	Lys	Thr 315	Phe	Arg	Thr	Thr	Phe 320
	Lys	Thr	Leu	Leu	Leu	Cys	Gln	Cys	Asp	Lys	Arg	Lys	Arg	Arg	Lys	Gln

40

BN 10 1000 HAR BRANCH

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325 330 335 Gln Tyr Gln Gln Arg Gln Ser Val Ile Phe His Lys Arg Val Pro Glu 345 Gln Ala Leu 5 355 (2) INFORMATION FOR SEQ ID NO:12: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 333 amino acids (B) TYPE: amino acid 10 (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12: Met Val Phe Ile Ala Thr Val Arg Gly Ser Leu Ser Leu Val Thr Val 15 Val Gly Asn Ile Leu Val Met Leu Ser Ile Lys Val Asn Arg Gln Leu Gln Thr Val Asn Asn Tyr Phe Leu Phe Ser Ile Ala Cys Ala Asp Leu 20 Ile Ile Gly Ala Phe Ser Met Asn Leu Tyr Thr Val Tyr Ile Ile Lys 55 Gly Tyr Trp Pro Lau Gly Ala Trp Cys Asp Leu Trp Leu Ala Leu Asp Tyr Val Val Ser Asn Ala Ser Val Met Leu Leu Ile Ile Ser Phe Asp 25 Arg Tyr Phe Cys Val Thr Lys Pro Leu Thr Tyr Pro Ala Arg Arg Thr Thr Lys Met Ala Gly Ile Met Ile Ala Ala Ala Trp Val Leu Ser Phe 30 Val Leu Trp Ala Pro Ala Ile Leu Phe Trp Gln Phe Val Val Gly Lys 135 Arg Thr Val Pro Asp Asn Gln Cys Phe Ile Gln Phe Leu Ser Asn Pro 155 Ala Val Thr Phe Gly Thr Ala Ile Ala Ala Phe Tyr Leu Pro Val Val 35 Ile Met Ile Val Leu Tyr Ile His Ile Ser Leu Ala Ser Arg Ser Arg 180

Ala Ile Leu Leu Ala Phe Ile Leu Thr Trp Thr Pro Tyr Asn Val Met

Val His Lys His Arg Pro Glu Gly Pro Lys Glu Lys Lys Ala Lys Thr

Ile Ala Phe Leu Lys Ser Pro Ile Met Gln Ser Val Lys Lys Pro Pro

Pro Gly Glu Ala Lys Phe Ala Ser Ile Ala Arg Asn Gln Val Arg Lys

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		Val	Leu	Val 275	Asn	Thr	Phe	Cys	Gln 280	Ser	Cys	Ile	Pro	Asp 285	Thr	Val	Trp
		Ser	Ile 290	Gly	Tyr	Trp	Leu	Ile 295	Cys	Tyr	Val	Asn	Ser 300	Thr	Ile	Asn	Pro
5		Ala 305	Cys	Tyr	Ala	Leu	Сув 310	Asn	Ala	Thr	Phe	Lys 315	Lys	Thr	Phe	Arg	His 320
		Leu	Leu	Leu	Cys	Gln 325	Arg	Tyr	Asn	Ile	Gly 330	Thr	Ala	Arg			
10	(2)	INFO	SEQI (A (B (C	ION : UENC:) LE:) TY!) ST!) TO!	E CHI NGTH PE: 8 RANDI	ARAC' : 34: amin EDNE:	TERIS 8 am: 0 ac: SS: s	STIC: ino a id sing:	S: acid	s							
15		(ii)															
		(xi) Val 1	SEQ1 Ile	UENCI Thr	E DE: Ile	SCRII Ala 5	PTION Val	N: SI Val	EQ II Thr	NO Ala	:13: Val 10	Val	Ser	Leu	Met	Thr 15	Ile
20		Val	Gly	Asn	Val 20	Leu	Val	Met	Ile	Ser 25	Phe	Lys	Val	Asn	Ser 30	Gln	Leu
		Lys	Thr	Val 35	Asn	Asn	Tyr	Tyr	Leu 40	Leu	Ser	Ile	Ala	Cys 45	Ala	Asp	Leu
		Ile	Ile 50	Gly	Ile	Phe	Ser	Met 55	Asn	Leu	Tyr	Thr	Thr 60	Tyr	Ile	Leu	Ile
25		Me t 65	Gly	Arg	Trp	Ala	Leu 70	Gly	Ser	Leu	Ala	Cys 75	qaA	Leu	Trp	Leu	Ala 80
		Ile	Asp	Tyr	Val	Ala 85	Ser	Asn	Ala	Ser	Val 90	Leu	Asn	Leu	Leu	Val 95	Ile
30		Ser	Phe	Asp	Arg 100	Tyr	Phe	Ser	Ile	Thr 105	Arg	Pro	Leu	Thr	Tyr 110	Arg	Ala
		Lys	Arg	Thr 115	Pro	Lys	Arg	Ala	Gly 120	Ile	Met	Ile	Gly	Ile 125	Ala	Trp	Leu
		Ile	Ser 130	Phe	Ile	Leu	Trp	Ala 135	Pro	Ala	Ile	Leu	Cys 140	Trp	Gln	Tyr	Leu
35		Val 145	Gly	Lys	Arg	Thr	Val 150	Pro	Ile	Asp	Glu	Cys 155	Gln	Ile	Gln	Phe	Leu 160
		Ser	Glu	Pro	Thr	Ile 165	Thr	Phe	Gly	Thr	Ala 170	Ile	Ala	Ala	Phe	Tyr 175	Ile
40		Pro	Val	Ser	Ile 180	Met	Arg	Ile	Leu	Tyr 185	Cys	Arg	Ile	Tyr	Arg 190	Glu	Thr
		Glu	Lys	Arg 195	Thr	Lys	Asp	Leu	Ala 200	Asp	Leu	Gln	Gly	Ser 205	Asp	Ser	Val
		Tyr	Lys 210	Ala	Glu	Lys	Arg	Lys 215	Pro	Ala	His	Arg	Ala 220	Leu	Phe	Arg	Ser
45		Cys 225	Leu	Arg	Cys	Pro	Arg 230	Pro	Thr	Lys	Gly	Leu 235	Asn	Pro	Asn	Pro	Ser 240
		His	Gln	Met	Thr	Iys	Arg	Lys	Arg	Met	Ser	Leu	Val	Lys	Glu	Arg	Lys

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						245					250					255	
		Ala	Ala	Gln	Thr 260	Leu	Ser	Ala	Ile	Leu 265	Leu	Ala	Phe	Ile	Ile 270	Thr	Trp
5		Thr	Pro	Tyr 275	Asn	Ile	Met	Val	Leu 280	Val	Ser	Thr	Phe	Cys 285	Asp	Lys	Cys
		Val	Pro 290	Val	Thr	Leu	Trp	His 295	Leu	Gly	Tyr	Trp	Leu 300	Cys	Tyr	Ile	Asn
		Ser 305	Thr	Val	Asn	Pro	Ile 310	Cys	Tyr	Ala	Leu	Cys 315	Asn	Arg	Thr	Phe	Arg 320
10		Lys	Thr	Phe	Ile	Met 325	Leu	Leu	Сув	Arg	Trp 330	Lys	Lys	Lys	Lys	Val 335	Glu
		Glu	Lys	Leu	Tyr 340	Trp	Gln	Gly	Asn	Ser 345	Lys	Leu	Pro				
15	(2)	INFOR	SEQUAL (A) (B) (C)	JENCI LEI TYI STI	E CHA NGTH: PE: & RANDE	SEQ 1 ARACT : 375 amino EDNES	reris 7 ami 5 aci 5S: s	STICS ino a id singl	S: acids	5							
20		(ii)															
		(xi) Thr 1	SEQU Ala	JENCE Gly	Asp	Cys 5	PTION Leu	N: SI Ile	EQ II M et	NO: Leu	14: Ile 10	Val	Leu	Leu	Ile	Val 15	Ala
25		Gly	naA	Val	Leu 20	Val	Ile	Val	Ala	Ile 25	Ala	Lys	Thr	Pro	Arg 30	Leu	Gln
		Thr	Leu	Thr 35	Asn	Leu	Phe	Ile	Met 40	Ser	Ile	Ala	Ser	Ala 45	Asp	Leu	Val
		Met	Leu 50	Leu	Leu	Val	Val	Pro 55	Phe	ayɔ	Ala	Thr	Leu 60	Val	Val	Trp	Gly
30		Arg 65	Trp	Glu	Tyr	Gly	Ser 70	Phe	Phe	Cys	Glu	Leu 75	Trp	Thr	Ser	Val	As p 80
		Val	Leu	Cys	Val	Thr 85	Ala	Ser	Ile	Glu	Thr 90	Leu	Cys	Val	Ile	Ala 95	Leu
35		Asp	Arg	Tyr	Leu 100	Ala	Ile	Thr	Ser	Pro 105	Phe	Arg	Tyr	Gln	Ser 110	Leu	Leu
		Thr	Arg	Ala 115	Arg	Äla	Arg	Gly	Leu 120	Val	Cys	Thr	Val	Trp 125	Ala	Ile	Ser
		Ala	Leu 130	Val	Ser	Phe	Leu	Pro 135	Ile	Leu	Leu	Ser	Asp 140	Glu	Ala	Arg	Arg
40		Cys 145	Tyr	Asn	qaA	Pro	Lys 150	Cys	Cys	Asp	Phe	Val 155	Thr	Asn	Arg	Ala	Tyr 160
		Ala	Ile	Ala	Ser	Ser	Val	Val	Ser	Phe	Tyr	Val	Pro	Leu	Cys	Tle	Met

Ile Asp Ser Cys Glu Arg Arg Phe Leu Gly Gly Pro Ala Arg Pro Pro 195 200 205

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		Ser	Pro 210	Ser	Pro	Ser	Pro	Val 215	Pro	Ala	Pro	Ala	Pro 220	Pro	Gly	Pro	Pro
		Arg 225	Pro	Ala	Ala	Ala	Ala 230	Ala	Thr	Ala	Pro	Leu 235	Ala	Asn	Gly	Arg	Ala 240
5		Gly	Lys	Arg	Arg	Pro 245	Ser	Arg	Leu	Val	Ala 250	Leu	Arg	Glu	Gln	Lys 255	Ala
		Leu	Lys	Thr	Leu 260	Gly	Ile	Ile	Met	Gly 265	Val	Phe	Thr	Leu	Cys 270	Trp	Leu
10		Pro	Phe	Phe 275	His	Arg	Glu	Leu	Val 280	Pro	Asp	Arg	Leu	Phe 285	Val	Phe	Phe
		Asn	Trp 290	Leu	Arg	Tyr	Ala	Asn 295	Ser	Ala	Phe	Asn	Pro 300	Ile	Ile	Tyr	Cys
		Arg 305	Ser	Pro	Asp	Phe	Arg 310	Lys	Ala	Phe	Gln	Gly 315	Leu	Leu	Cys	Сув	Ala 320
15		Arg	Arg	Ala	Ala	Arg 325	Arg	Arg	His	Ala	Thr 330	His	Gly	Asp	Arg	Pro 335	Arg
					340			Arg		345					350		
20				355				Asp	360		Gly	Ala	Thr	Pro 365	Pro	Ala	Arg
			370					Gly 375		Asn							
	(2) I	NEOL	יידי או או	ו זארה	(A)	ירים י	T 37/	1.1E									
25		(i)	(A) (B) (C) (D)	JENCE LEN TYP	E CHA NGTH: PE: & RANDE POLOC	ARACT : 362 mino EDNES SY:]	reris 2 am 3 ac: 3S: s Lines	STICS ino a id singl	S: acids	5							
25 30	((i) ii) xi)	SEQUAL (B) (C) (D) MOLE	JENCE TYPE STE TOE CULE JENCE	E CHA NGTH: PE: & RANDE POLOGE TYPE DES	ARACT 362 mino EDNES SY: 1 PE: p	TERIS ami aci ss: lines pepti PTION	STICS ino a id singl	S: acids le EQ II	o no:	:15: Val 10	Leu	Ala	Ile	Val	Phe 15	Gly
	((i) ii) xi) Val	SEQU (A) (B) (C) (D) MOLE SEQU Val	JENCE TYPE TOPE TOPE ECULE JENCE Gly	E CHANGTH: PE: a RANDE POLOG E TYPE L DES	ARACT 362 amino EDNES SY: 1 PE: p CCRIE Val	TERIS ami acc SS: line pepti PTION Met	STICS ino a id singl ar ide	S: acids le EQ II Leu	NO: Ile	Val 10					15	_
	((i) ii) xi) Val 1 Asn	SEQUANCE (A) (B) (C) (D) MOLE SEQUANCE Val	JENCE TYPE STE TOPE ECULE JENCE Gly Leu	E CHANGTH: PE: a RANDE POLOG E TYPE L DES Ile Val 20	ARACT : 362 amino EDNES GY: 1 PE: p CCRIF Val 5	TERIS 2 am: 2 ac: 3 ac: 35: 5 sines 6 pept: 7TION Met Thr	STICS ino a id singl ar ide N: SE Ser	S: acids le EQ II Leu Ile	NO: Ile Ala 25	Val 10 Lys	Phe	Glu	Arg	Leu 30	15 Gln	Thr
30	((i) ii) xi) Val 1 Asn	SEQUE (A) (B) (C) (D) MOLE SEQUE Val Val	JENCE LEN TYPE TOPE CULE Gly Leu Asn 35	E CHANGTH: PE: a RANDE POLOG E TYPE L DES Lle Val 20 Tyr	ARACT 362 amino EDNES SY: 1 PE: p SCRIF Val 5 Ile Phe	TERIS 2 am: 5 ac: 5S: 5S: 5S: 5PTION Met Thr	STICS ino a id singl ar ide N: SE Ser Ala	S: acids le EQ II Leu Ile Ser 40	NO: Ile Ala 25 Ile	Val 10 Lys Ala	Phe Cys	Glu Ala	Arg Asp 45	Leu 30 Leu	15 Gln Val	Thr Met
30	((i) ii) xi) Val 1 Asn Val	SEQUANDLE SEQUENDLE SEQUEN	JENCE LEN TYPE TOPECULE Gly Leu Asn 35	E CHANGTH: PE: a RANDE POLOG E TYF C DES Ile Val 20 Tyr	ARACT 362 amino EDNES SY: 1 PE: p CCRIF Val 5 Ile Phe Val	TERIS ami accidents accidents Example 100 Met Thr Ile Pro	STICS ino a id singl ir ide N: SI Ser Ala Thr	S: acids le EQ II Leu Ile Ser 40 Gly	NO: Ile Ala 25 Ile Ala	Val 10 Lys Ala Ala	Phe Cys His	Glu Ala Ile 60	Arg Asp 45 Leu	Leu 30 Leu Met	15 Gln Val Lys	Thr Met
30	((i) ii) xi) Val l Asn Val Gly Trp 65	SEQUAL (A) (B) (C) (D) MOLE SEQUAL Val Thr	JENCE LEN TYI TOI TOI Gly Leu Asn 35	E CHARGE CHARACTER AND E TYPE I DESTILLE CONTROL TYPE Val CONTROL CONT	ARACT 362 amino EDNES SY: 1 PE: F SCRIF Val 5 Ile Phe Val Asn	PTION Met Thr Ile Pro Phe 70	STICS ino a id singl ir ide N: SI Ser Ala Thr	S: acids le EQ II Leu Ile Ser 40 Gly Cys	NO: Ile Ala 25 Ile Ala Glu	Val 10 Lys Ala Ala	Phe Cys His Trp 75	Glu Ala Ile 60 Thr	Arg Asp 45 Leu Ser	Leu 30 Leu Met	15 Gln Val Lys Asp	Thr Met Met Val 80
30	((i) ii) xi) Val Asn Val Gly Trp 65	SEQUANCE (A) (B) (C) (D) MOLE SEQUANCE (C) Val Thr Leu 50 Thr Cys	JENCE TYPE TOPE CULE JENCE Gly Leu Asn 35 Ala Phe Val	E CHARGE CHARACTER AND E TYPE C DESTRUCTION TYPE C DESTRUCTOR TYPE C DESTRUCTOR C TYPE C DESTRUCTOR C DESTRUC	ARACTOR 362 amino EDNESSY: 1 PE: F SCRIF Val 5 Ile Val Asn Ala 85	TERISE AMEDICAL SS: SINGE SS: SINGE SOEPTION MET Thr Ile Pro Phe 70 Ser	STICS ino a id singl ar ide N: SE Ser Ala Thr Phe 55 Trp	S: acids le EQ II Leu Ile Ser 40 Gly Cys	NO NO Ile Ala 25 Ile Ala Glu Thr	Val 10 Lys Ala Ala Phe Leu 90	Phe Cys His Trp 75 Cys	Glu Ala Ile 60 Thr	Arg Asp 45 Leu Ser	Leu 30 Leu Met Ile	15 Gln Val Lys Asp Val 95	Thr Met Met Val 80 Asp
30	((ii) iii) xii) Val 1 Asn Val Gly Trp 65 Leu Arg	SEQUANCE (A) (B) (C) (D) MOLE SEQUANCE (C) Val Thr Cys	JENCE LEN TYPE TOPE GOVERNMENT	E CHAIGTH: PE: a RANDE POLOG E TYPE Val 20 Tyr Val Gly Thr Ala 100	ARACTOR 362 amino EDNESSY: I PE: F Val Phe Val Asn Ala 85 Ile	TERISE AMES ACTION MET THE Pro Phe 70 Ser	STICS ino a id singl ir ide N: SI Ser Ala Thr Phe 55 Trp Ile	S: acids le EQ II Leu Ile Ser 40 Gly Cys Glu Pro	NO NO Ile Ala 25 Ile Ala Glu Thr	Val 10 Lys Ala Ala Phe Leu 90 Lys	Phe Cys His Trp 75 Cys	Glu Ala Ile 60 Thr Val Gln	Arg Asp 45 Leu Ser Ile	Leu 30 Leu Met Ile Ala	15 Gln Val Lys Asp Val 95 Leu	Thr Met Wet Val 80 Asp

 $\{P(p^{*})\} \mapsto \{1,\dots,N_{n}\} = 94^{n} \operatorname{max}(A)$

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			130					135					140				
		Ile 145	Asn	Cys	Tyr	Ala	Asn 150	Glu	Thr	Cys	Cys	Asp 155	Phe	Phe	Thr	Asn	Gln 160
5		Ala	Tyr	Ala	Ala	Ser 165	Ser	Ala	Val	Ser	Phe 170	Tyr	Val	Pro	Leu	Val 175	Ile
		Met	Val	Phe	Val 180	Tyr	Ser	Arg	Val	Phe 185	Gln	Glu	Ala	Lys	Arg 190	Gln	Leu
		Gln	Lys	Ile 195	qaA	Lys	Ser	Glu	Gly 200	Arg	Phe	Ile	Phe	Val 205	Gln	Asn	Leu
10		Ser	Gln 210	Val	Glu	Gln	qaA	Gly 215	Arg	Thr	Gly	His	Gly 220	Leu	Arg	Arg	Ser
		Ser 225	Lys	Phe	Cys	Leu	Lys 230	Glu	His	Lys	Ala	Leu 235	Lys	Thr	Leu	Gly	Ile 240
15		Ile	Pro	Cys	Thr	Phe 245	Thr	Leu	Cys	Trp	Leu 250	Pro	Phe	Phe	Ile	Val 255	Asn
		Ile	Val	Val	Ile 260	Gln	Asp	Asn	Leu	Ile 265	Arg	Lys	Glu	Val	Tyr 270	Ile	Leu
	,	Leu	Asn	Trp 275	Ile	Gly	Tyr	Val	Asn 280	Ser	Gly	Phe	Asn	Pro 285	Leu	Ile	Tyr
20		Cys	Arg 290	Ser	Pro	Asp	Phe	Arg 295	Ile	Ala	Phe	Gln	Glu 300	Leu	Leu	Cys	Leu
		Arg 305	Arg	Ser	Ser	Leu	Lys 310	Ala	Tyr	Gly	Asn	Gly 315	Tyr	Ser	Ser	Asn	Gly 320
25		Asn	Thr	Gly	Glu	Gln 325	Ser	Gly	Tyr	His	Val 330	Glu	Gln	Glu	Lys	Glu 335	Asn
		Lys	Leu	Leu	Cys 3 4 0	Glu	Asp	Leu	Pro	Gly 3 4 5	Thr	Glu	Asp	Phe	Val 350	Gly	His
		Gln	Gly	Thr 355	Val	Pro	Ser	Asp	Asn 360	Ile	qaA						
30	(2)	INFO	SEQI (A)	ION DENCION DE LE	E CHA NGTH PE: 8	ARAC' : 36: amin	reris 2 am: 5 ac:	STIC: ino a id	S: acid:	5							
35		(ii)) TOI													
			_	JENC! Leu					_			Ala	Val	Leu	Ala	Thr 15	Val
40		Gly	Gly	Asn	Leu 20	Leu	Val	Ile	Val	Ala 25	Ile	Ala	Trp	Thr	Pro 30	Arg	Leu
		Gln	Thr	Met	Thr	Asn	Val	Phe	Val	Thr	Ser	Leu	Ala	Ala	Ala	Asp	Leu

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		Leu	Cys	Val	Thr	Ala 85	Ser	Ile	Glu	Thr	Leu 90	Cys	Ala	Ile	Ala	Val 95	Asp
		Arg	Tyr	Leu	Ala 100	Val	Thr	Asn	Pro	Leu 105	Arg	Tyr	Gly	Ala	Leu 110	Val	Thr
5		Lys	Arg	Cys 115	Ala	Arg	Thr	Ala	Trp 120	Leu	Val	Trp	Val	Val 125	Ser	Ala	Ala
		Val	Ser 130	Phe	Ala	Pro	Ile	Met 135	Ser	Gln	Trp	Trp	Arg 140	Val	Gly	Ala	Asp
10		Ala 145	Glu	Ala	Gln	Arg	Cys 150	His	Ser	Asn	Pro	Arg 155	Cys	Cys	Ala	Phe	Ala 160
		Ser	Asn	Met	Pro	Tyr 165	Ala	Val	Leu	Leu	Ser 170	Ser	Ser	Val	Ser	Phe 175	Tyr
		Leu	Pro	Leu	Leu 180	Leu	Phe	Val	Tyr	Ala 185	Arg	Val	Phe	Trp	Ala 190	Thr	Arg
15		Gln	Leu	Arg 195	Leu	Leu	Arg	Gly	Glu 200	Leu	Gly	Arg	Phe	Pro 205	Pro	Glu	Glu
		Ser	Pro 210	Pro	Ala	Pro	Ser	Arg 215	Ser	Leu	Ala	Pro	Ala 220	Pro	Val	Gly	Thr
20		Gly 225	Ala	Pro	Pro	Glu	Gly 230	Val	Pro	Ala	Cys	Gly 235	Arg	Pro	Pro	Ala	Arg 240
		Leu	Ile	Pro	Ile	Arg 245	Glu	His	Arg	Ala	Leu 250	Cys	Thr	Leu	Gly	Leu 255	Ile
		Met	Gly	Thr	Phe 260	Thr	Leu	Cys	Trp	Leu 265	Pro	Phe	Phe	Ile	Ala 270	Asn	Val
25		Leu	Arg	Ala 275	Leu	Gly	Gly	Pro	Ser 280	Leu	Val	Pro	Gly	Pro 285	Ala	Phe	Leu
		Ala	Leu 290	Asn	Trp	Leu	Ile	Gly 295	Tyr	Ala	Asn	Ser	Ala 300	Phe	Asn	Pro	Leu
30		Ile 305	Tyr	Cys	Arg	Ser	Pro 310	Asp	Phe	Arg	Ser	Ala 315	Phe	Arg	Arg	Leu	Leu 320
		Сув	Arg	Cys	Gly		_	Leu					Cys		Ala	Ala 335	Arg
		Pro	Ala	Leu	Phe 340	Pro	Ser	Gly	Val	Pro 345	Ala	Ala	Glu	Ser	Ser 350	Pro	Ala
35		Gln	Pro	Arg 355	Leu	Cys	Gln	Arg	Leu 360	Asp	Gly						
40	(2)	INFOI (i)	SEQUAL (A)	JENCI) LEI) TYI) STI) TOI	E CHI NGTH PE: 8 RANDI POLO	ARACT 375 amino EDNE: 3Y:	reris 5 am: 5 ac: 5S: 1	STIC: ino a id sing: ar	S: acid:	5							
45		(xi) Ala 1		JENCI Leu								Leu	Ile	Leu	Phe	Gly 15	Val
		Leu	Gly	Asn	Ile	Leu	Val	Ile	Leu	Ser	Val	Ala	Cys	His	Arg	His	Leu

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				20					25					30		
	His	Ser	Val 35	Thr	His	Tyr	Tyr	Ile 40	Val	Asn	Leu	Ala	Val 45	Ala	Asp	Leu
5	Leu	Leu 50	Thr	Ser	Thr	Val	Leu 55	Pro	Phe	Ser	Ala	Ile 60	Phe	Glu	Ile	Leu
	Gly 65	Tyr	Trp	Lys	Phe	Gly 70	Arg	Val	Phe	Cys	Asn 75	Val	Trp	Ala	Ala	Val 80
	Asp	Val	Leu	Cys	Cys 85	Thr	Ala	Ser	Ile	Met 90	Leu	Leu	Cys	Ile	Ile 95	Ser
10	Ile	qaA	Arg	Tyr 100	Ile	Gly	Val	Ser	Tyr 105	Pro	Leu	Arg	Tyr	Pro 110	Thr	Ile
	Val	Thr	Gln 115	Lys	Arg	Gly	Leu	Met 120	Ala	Leu	Leu	Cys	Val 125	Trp	Ala	Leu
15	Ser	Leu 130	Val	Ile	Ser	Ile	Gly 135	Pro	Leu	Phe	Gly	Trp 140	Arg	Gln	Pro	Ala
	Pro 145	Glu	Asp	Glu	Thr	Ile 150	Сув	Gln	ıle	Asn	Glu 155	Glu	Pro	Gly	Tyr	Val 160
	Leu	Phe	Ser	Ala	Leu 165	Gly	Ser	Phe	Tyr	Val 170	Pro	Leu	Thr	Ile	Ile 175	Leu
20	Val	Met	Tyr	Cys 180	Arg	Val	Tyr	Val	Val 185	Ala	Lys	Arg	Glu	Ser 197	Arg	Gly
	Leu	Lys	Ser 195	Gly	Leu	Lys	Thr	Asp 200	Lys	Ser	Asp	Ser	Glu 205	Gln	Val	Thr
25	Leu	Arg 210	Ile	His	Arg	Lys	Asn 215	Ala	Gln	Val	Gly	Gly 220	Ser	Gly	Val	Thr
	Ser 225	Ala	Lys	Asn	Lys	Thr 230	His	Phe	Ser	Val	Arg 235	Leu	Leu	Lys	Phe	Ser 240
	Arg	Glu	Lys	Lys	Ala 2 4 5	Ala	Lys	Thr	Leu	Gly 250	Ile	Val	Val	Gly	Cys 255	Phe
30	Val	Leu	Cys	Trp 260	Leu	Pro	Phe	Phe	Leu 265	Val	Met	Pro	Ile	Gly 270	Ser	Phe
	Phe	Pro	Asp 275	Phe	Arg	Pro	Ser	Glu 280	Thr	Val	Phe	Lys	Ile 285	Ala	Phe	Trp
35	Leu	Gly 290		Ile	Asn	Ser	Cys 295	Ile	Asn	Pro	Ile	Ile 300		Pro	Cys	Ser
	Ser 305	Gln	Glu	Phe	Lys	Lys 310	Ala	Phe	Gln	Asn	Val 315	Leu	Arg	Ile	Gln	Cys 320
	Leu	Arg	Arg	Lys	Gln 325	Ser	Ser	Lys	His	Thr 330		Gly	Tyr	Thr	Leu 335	His
40	Ala	Pro	Ser	His	Val	Leu	Glu	Gly	Gln	His	Lys	Asp	Leu	Val	Arg	Ile

(2) INFORMATION FOR SEQ ID NO:18:

5	(2)	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 370 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide															
10		(xi) Ala 1										Phe	Ile	Leu	Phe	Ala 15	Ile
		Val	Gly	Asn	Ile 20	Leu	Val	Ile	Leu	Ser 25	Val	Ala	Cys	Asn	Arg 30	His	Leu
,		Arg	Thr	Pro 35	Thr	Asn	Tyr	Phe	Ile 40	Val	Asn	Ile	Ala	Ile 45	Ala	Asp	Leu
15		Leu	Leu 50	Ser	Phe	Thr	Val	Leu 55	Pro	Phe	Ser	Ala	Thr 60	Leu	Glu	Val	Leu
		Gly 65	Tyr	Trp	Val	Leu	Gly 70	Arg	Ile	Phe	Cys	As p 75	Ile	Trp	Ala	Ala	Val 80
20		Asp	Val	Leu	Cys	Cys 85	Thr	Ala	Ser	Ile	Leu 90	Ser	Leu	Cys	Ala	Ile 95	Ser
		Ile	Asp	Arg	Tyr 100	Ile	Gly	Val	Arg	Tyr 105	Ser	Leu	Gln	Tyr	Pro 110	Thr	Leu
		Val	Thr	Arg 115	Arg	Tyr	Ala	Ile	Ile 120	Ala	Leu	Leu	Ser	Val 125	Trp	Val	Leu
25		Ser	Thr 130	Val	Ile	Ser	Ile	Gly 135	Pro	Leu	Leu	Gly	Trp 140	Lys	Glu	Pro	Ala
		Pro 145	Asn	Asp	Asp	Lys	Glu 150	Cys	Val	Thr	Glu	Glu 155	Pro	Phe	Leu	Phe	Cys 160
30			Leu			165					170					175	_
			Arg		180					185					190		
			Val	195					200					205			
35			Trp 210					215					220				
		225	Gly				230					235					240
40			Arg			245					250					255	_
			Leu		260					265					270		
4.5			Ser	275					280					285			
45			Tyr 290					295					300				
		Lys	Glu	Phe	Lys	Arg	Ala	Leu	Leu	Gly	Cys	Gln	Cys	Arg	Gly	Gly	Arg

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		305					310					315					320
		Arg	Arg	Arg	Arg	Arg 325	Arg	Arg	Leu	Ala	Cys 330	Ala	Tyr	Thr	Tyr	Arg 335	Pro
5		Trp	Thr	Arg	Gly 340	Gly	Ser	Leu	Glu	Arg 345	Ser	Gln	Ser	Arg	Lys 350	Asp	Ser
		Ile	Asp	Asp 355	Ser	Gly	Ser	Cys	Met 360	Ser	Gly	Gln	Lys	Arg 365	Thr	Leu	Pro
		Ser	Ala 370														
10	(2)	INFOR	SEQU (A) (B)		CHA IGTH: PE: 4	ARĀCI 330 amino	TERIS ami	TICS no a ld	S: acids	5							
15		(ii)	(D)	TOE	OLO	3 Y:]	linea	ar	·e								
		(xi) Val l	SEQU Ala									Leu	Ile	Val	Phe	Thr	Val
20			Gly	naA	Val 20	_	Val	Val	Ile	Ala 25		Leu	Thr	Ser	Arg		Leu
		Arg	Ala	Pro 35		Asn	Leu	Phe	Leu 40		Ser	Ile	Ala	Ser 45	Ala	Asp	Ile
25		Leu	Val 50	Ala	Thr	Leu	Val	Met 55	Pro	Phe	Ser	Leu	Ala 60	Asn	Glu	Ile	Met
		Tyr 65	Trp	Tyr	Phe	Gly	Gln 70	Val	Trp	Сув	Gly	Val 75	Tyr	Leu	Ala	Ile	Asp 80
		Val	Leu	Phe	Сув	Thr 85	Ser	Ser	Ile	Val	His 90	Leu	Cys	Ala	Ile	Ser 95	Leu
30		Asp	Arg	Tyr	Trp 100	Ser	Val	Thr	Gln	Ala 105	Val	Glu	Tyr	Asn	Leu 110	Lys	Arg
		Thr	Pro	Ar g 115	Arg	Val	Lys	Ala	Thr 120	Ile	Val	Ala	Val	Trp 125	Leu	Ile	Ser
35		Ala	Val 130	Ile	Ser	Phe	Pro	Pro 135	Leu	Val	Ser	Leu	Tyr 140	Arg	Gln	Pro	Asp
		Gly 145	Ala	Ala	Tyr	Pro	Gln 150	Cys	Gly	Leu	Asn	Asp 155	Glu	Thr	Trp	Tyr	Ile 160
		Leu	Ser	Ser	Cys	Ile 165	Gly	Ser	Phe	Phe	Ala 170		Сув	Leu	Ile	Tyr 175	Leu
40		Leu	Val	Tyr	Ala 180	Arg	Ile	Tyr	Arg	Val 185		Lys	Arg	Arg	Thr 190	Arg	Thr
		Leu	Ser	Glu 195	Lys	Arg	Ala	Pro	Val 200		Pro	Asp	Gly	Ala 205		Pro	Thr
		-: .	~ •	•	~~	-	~*	-	• • -	• • •	G 7	יי	113	*,	mL	73	mu.

Arg Lys Val Ala Gln Ala Arg Glu Lys Arg Phe Thr Phe Val Leu Ala

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						245					250					255	
		Leu	Val	Phe	Val 260	Leu	Cys	Trp	Phe	Pro 265	Phe	Phe	Phe	Ile	Tyr 270	Ser	Leu
5		Tyr	Gly	Ile 275	Cys	Arg	Glu	Ala	Cys 280	Gln	Val	Pro	Gly	Pro 285	Leu	Phe	Lys
		Phe	Phe 290	Phe	Trp	Ile	Gly	Tyr 295	Cys	Asn	Ser	Ser	Leu 300	Asn	Pro	Val	Ile
		Tyr 305	Thr	Val	Phe	Asn	Gln 310	Asp	Phe	Arg	Pro	Ser 315	Phe	Lys	His	Ile	Leu 320
10		Phe	Arg	Arg	Arg	Arg 325	Arg	Gly	Phe	Arg	Gln 330						
15	(2)		SEQU (A) (B) (C) (D)	JENCI LEI TYI STI	E CHI NGTH PE: & RANDI POLO	ARACT 330 amino EDNES	ID NO TERIS O am: O ac: SS: s lines pept:	STICS ino a id sing: ar	S: acids	5							
		(xi)	SEQ	JENCI	E DES	SCRI	PTIO	N: SI	EQ II	ON C	:20:						
20		Thr 1	Ala	Ala	Ile	Ala 5	Ala	Ala	Ile	Thr	Phe 10	Leu	Ile	Leu	Phe	Thr 15	Ile
		Phe	Gly	Asn	Ala 20	Leu	Val	Ile	Ile	Ala 25	Val	Leu	Thr	Ser	Arg 30	Ser	Leu
25		Arg	Ala	Pro 35	Gln	Asn	Leu	Phe	Leu 40	Val	Ser	Ile	Ala	Ala 45	Ala	Asp	Ile
		Leu	Val 50	Ala	Thr	Leu	Ile	Ile 55	Pro	Phe	Ser	Leu	Ala 60	Asn	Glu	Leu	Leu
		Gly 65	Tyr	Trp	Tyr	Phe	Arg 70	Arg	Thr	Trp	Cys	Glu 75	Val	Tyr	Leu	Ala	Leu 80
30		Asp	Val	Leu	Phe	Cys 85	Thr	Ser	Ser	Ile	Val 90	His	Leu	Cys	Ala	Ile 95	Ser
		Leu	Asp	Arg			Ala										Lys
35		Arg	Thr	Pro 115	Arg	Arg	Ile	Lys	Cys 120	Ile	Ile	Leu	Thr	Val 125	Trp	Leu	Ile
		Ala	Ala 130	Val	Ile	Ser	Leu	Pro 135	Pro	Leu	Ile	Tyr	Lys 140	Gly	Asp	Gln	Gly
		Pro 145	Gln	Pro	Arg	Gly	Arg 150	Pro	Gln	Cys	Lys	Leu 155	Asn	Gln	Glu	Ala	Trp 160
40		Tyr	Ile	Leu	Ser	Ser 165	Ile	Gly	Ser	Phe	Phe 170	Ala	Pro	Cys	Leu	Ile 175	Leu
		Leu	Val	Tyr	Leu 180	Arg	Ile	Tyr	Leu	Ile 185	Ala	Lys	Arg	Ser	Asıı 190	Arg	Arg
45		Gly	Pro	Arg 195	Ala	∟ys	Cys	Gly	Pro 200	Gly	Gln	Gly	Glu	Ser 205	Lys	Gln	Pro
		Arg	Pro	qaA	His	Gly	Gly	Ala	Ile	Ala	Ser	Ala	Lys	Leu	Pro	Ala	Ile

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			210					215					220				
		Ala 225	Ser	Gly	Arg	Gly	Val 230	Gly	Ala	Ile	Gly	Gly 235	Gln	Trp	Trp	Arg	Arg 240
5		Arg	Ala	His	Val	Thr 245	Arg	Glu	Lys	Arg	Phe 250	Thr	Phe	Val	Leu	Ala 255	Val
		Val	Ile	Gly	Val 260	Phe	Val	Leu	Cys	Trp 265	Phe	Pro	Phe	Phe	Phe 270	Ser	Tyr
		Ser	Leu	Gly 275	Ala	Ile	Cys	Pro	Lys 280	His	Cys	Lys	Val	Pro 285	His	Gly	Leu
10		Phe	Gln 290	Phe	Phe	Phe	Trp	Ile 295	Gly	Tyr	ayɔ	Asn	Ser 300	Ser	Leu	Asn	Pro
		Val 305	Ile	Tyr	Thr	Ile	Phe 310	Asn	Gln	qaA	Phe	Arg 315	Met	Phe	Arg	Arg	Ile 320
15		Leu	Cys	Arg	Pro	Trp 325	Thr	Gln	Thr	Ala	Trp 330						
20	(2)	INFOR	SEQU (A) (B) (C) (D)	JENCH LEI TYI STI	E CHANGTH: PE: 6 RANDI POLOG	ARACT : 330 emino EDNES EY: 1	TERIS ami aci SS: s linea	STICS ino a id sing! ar	S: acids	5							
25		(xi) Thr 1		JENCI Thr								Ser	Leu	Thr	Val	Phe 15	Gly
		Asn	Val	Leu	Val 20	Ile	Ile	Ala	Val	Phe 25	Thr	Ser	Arg	Ala	Leu 30	Lys	Ala
		Pro	Gln	Asn 35	Leu	Phe	Leu	Val	Ser 40	Ile	Ala	Ser	Ala	Asp 45	Ile	Leu	Val
30		Ala	Thr 50	Leu	Val	Ile	Pro	Phe 55	Ser	Leu	Ala	Asn	Glu 60	Val	Asn	Gly	Tyr
		Trp 65	Tyr	Phe	Gly	Lys			Glu			Leu 75	Ala	Leu	Asp	Val	Leu 80
35		Phe	Cys	Thr	Ser	Ser 85	Ile	Val	His	Leu	Cys 90	Ala	Ile	Ser	Leu	Asp 95	Arg
		Tyr	Trp	Ser	Ile 100	Thr	Gln	Ala	Ile	Glu 105	Tyr	Asn	Leu	Lys	Arg 110	Thr	Pro
		Arg	Arg	Ile 115	Lys	Ala	Ile	Ile	Ile 120	Thr	Val	Trp	Val	Ile 125	Ser	Ala	Val
40		Ile	Ser 130	Phe	Pro	Pro	Leu	Ile 135	Ser	Ile	Glu	Lys	Lys 140	Gly	Gly	Gly	Gly
		Gly	Pro	Gln	Pro	Ala	Glu	Pro	Arg	Cys	Glu	Ile	Asn	qaA	Gln	Lys	Trp
				Val													

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		Val	Pro	Pro 195	Ser	Arg	Arg	Asp	Pro 200	Asp	Ala	Val	Ala	Ala 205	Pro	Pro	Gly
		Gly	Thr 210	Glu	Arg	Arg	Pro	Asn 215	Gly	Leu	Gly	Pro	Glu 220	Arg	Ser	Ala	Gly
5		Pro 225	Gly	Gly	Gly	Arg	Gly 230	Arg	Ser	Ala	Ser	Gly 235	Leu	Pro	Arg	Arg	Arg 240
		Ala	Gly	Ala	Gly	Gly 245	Gln	Asn	Arg	Glu	Lys 250	Arg	Phe	Thr	Phe	Val 255	Ile
10		Ala	Val	Val	Ile 260	Gly	Val	Phe	Val	Val 265	Cys	Trp	Phe	Pro	Phe 270	Phe	Phe
		Thr	Tyr	Thr 275	Leu	Thr	Ala	Val	Leu 280	Cys	Ser	Val	Pro	Arg 285	Thr	Leu	Phe
		Lys	Phe 290	Phe	Phe	Trp	Phe	Gly 2 9 5	Tyr	Сув	Asn	Ser	Ser 300	Leu	Asn	Pro	Val
15		Ile 305	Tyr	Thr	Ile	Phe	Asn 310	His	Asp	Phe	Arg	Arg 315	Ala	Phe	Lys	Lys	Ile 320
		Leu	Cys	Arg	Gly	Asp 325	Arg	Lys	Arg	Ile	Val 330						
20	(2)	INFOR	SEQUAL (A)		E CHA NGTH: PE: 8	ARĀC : 334 amino	reris Lam: cac:	STICS ino a id	S: acids	5							
			(D)	TOE	POLO	3Y: :	linea	ar									
25		(ii)	MOL	ECULI	TYI	?E: p	pept:	ide									
25		(xi)		JENCI	E DES	SCRI	TIO	1: SI				Ile	Met	Leu	Ph∈	Thr 15	Val
30		(xi) Thr 1	SEQ	JENC! Thr	E DES Leu	SCRII Val 5	OITS Cys	N: SI Ile	Ala	Gly	Leu 10					15	
		(xi) Thr 1	SEQU Leu	JENCE Thr Asn	E DES Leu Val 20	SCRII Val 5	PTION Cys Val	N: SI Ile Ile	Ala	Gly Ala 25	Leu 10 Val	Phe	Thr	Ser	Arg 30	15 Ala	Leu
		(xi) Thr 1 Phe Lys	SEQU Leu	JENCE Thr Asn Pro	Leu Val 20	SCRII Val 5 Leu Asn	PTION Cys Val Leu	N: SI Ile Ile Phe	Ala Ile Leu 40	Gly Ala 25 Val	Leu 10 Val Ser	Phe Ile Leu	Thr Ala	Ser Ser 45	Arg 30 Ala	15 Ala Asp	Leu Ile
		(xi) Thr 1 Phe Lys	SEQU Leu Gly Ala Val	JENCE Thr Asn Pro 35	Leu Val 20 Gln	SCRII Val 5 Leu Asn	PTION Cys Val Leu Val	N: SI Ile Ile Phe Ile 55	Ala Ile Leu 40 Pro	Gly Ala 25 Val Phe	Leu 10 Val Ser	Phe Ile Leu	Thr Ala Ala 60	Ser Ser 45 Asn	Arg 30 Ala Glu	15 Ala Asp Val	Leu Ile Met
30		(xi) Thr 1 Phe Lys Leu Tyr 65	SEQU Leu Gly Ala Val	DENCE Thr Asn Pro 35 Ala	Val 20 Gln Thr	SCRII Val 5 Leu Asn Leu	Val Leu Val Lys	N: SI Ile Ile Phe Ile 55	Ala Ile Leu 40 Pro	Gly Ala 25 Val Phe Cys	Leu 10 Val Ser Ser	Phe Ile Leu Ile 75	Thr Ala Ala 60 Tyr	Ser Ser 45 Asn Leu	Arg 30 Ala Glu Ala	15 Ala Asp Val Ile	Leu Ile Met Asp
30		(xi) Thr 1 Phe Lys Leu Tyr 65 Val	SEQU Leu Gly Ala Val 50	JENCE Thr Asn Pro 35 Ala Tyr	Val 20 Gln Thr	SCRII Val 5 Leu Asn Leu Gly	Val Leu Val Lys 70 Ser	N: SI Ile Ile Phe Ile 55 Val	Ala Ile Leu 40 Pro Trp	Gly Ala 25 Val Phe Cys Val	Leu 10 Val Ser Ser Glu His 90	Phe Ile Leu Ile 75	Thr Ala Ala 60 Tyr Cys	Ser Ser 45 Asn Leu Ala	Arg 30 Ala Glu Ala Ile	Ala Asp Val Ile Ser	Leu Ile Met Asp 80 Leu
30		(xi) Thr 1 Phe Lys Leu Tyr 65 Val	SEQU Leu Gly Ala Val 50 Trp Leu	Pro 35 Ala Tyr Phe	Val 20 Gln Thr Phe Cys	CCRIN Val 5 Leu Asn Leu Gly Thr 85 Ser	Val Leu Val Lys 70 Ser	N: SI Ile Ile Phe Ile 55 Val Ser	Ala Ile Leu 40 Pro Trp Ile Gln	Gly Ala 25 Val Phe Cys Val Ala 105	Leu 10 Val Ser Ser Glu His 90 Ile	Phe Ile Leu Ile 75 Leu Glu	Thr Ala Ala 60 Tyr Cys	Ser Ser 45 Asn Leu Ala Asn	Arg 30 Ala Glu Ala Ile Leu	Ala Asp Val Ile Ser 95 Lys	Leu Ile Met Asp 80 Leu
30		(xi) Thr 1 Phe Lys Leu Tyr 65 Val Asp	SEQU Leu Gly Ala Val 50 Trp Leu Arg	Pro 35 Ala Tyr Phe Tyr Arg	Val 20 Gln Thr Phe Cys	CCRIN Val 5 Leu Asn Leu Gly Thr 85 Ser	Val Leu Val Lys 70 Ser Ile	N: SI Ile Ile Phe Ile 55 Val Ser Thr	Ala Ile Leu 40 Pro Trp Ile Gln Ile 120	Gly Ala 25 Val Phe Cys Val Ala 105 Ile	Leu 10 Val Ser Ser Glu His 90 Ile Val	Phe Ile Leu Ile 75 Leu Glu Thr	Thr Ala Ala 60 Tyr Cys Tyr Val	Ser Ser 45 Asn Leu Ala Asn Trp 125	Arg 30 Ala Glu Ala Ile Leu 110 Val	Ala Asp Val Ile Ser 95 Lys Ile	Leu Ile Met Asp 80 Leu
30		(xi) Thr 1 Phe Lys Leu Tyr 65 Val Asp Thr	SEQUENCE SEQ	JENCE Thr Asn Pro 35 Ala Tyr Phe Tyr Arg 115	Val 20 Gln Thr Phe Cys Trp 100 Arg	CCRING Val 5 Leu Asn Leu Gly Thr 85 Ser Ile	Val Leu Val Lys 70 Ser Ile Lys	N: SI Ile Ile Phe Ile 55 Val Ser Thr Ala Pro	Ala Ile Leu 40 Pro Trp Ile Gln Ile 120 Leu	Gly Ala 25 Val Phe Cys Val Ala 105 Ile Leu	Leu 10 Val Ser Ser Glu His 90 Ile Val	Phe Ile Leu Ile 75 Leu Glu Thr	Thr Ala Ala 60 Tyr Cys Tyr Val Ile 140	Ser Ser 45 Asn Leu Ala Asn Trp 125 Glu	Arg 30 Ala Glu Ala Ile Leu 110 Val	Ala Asp Val Ile Ser 95 Lys Ile Lys	Leu Ile Met Asp 80 Leu Arg Ser Gly

 $p(s_{k+1}) = c(f) + p_{k+1} = - (a_k) \theta(a_k) d(A) f.$

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						165					170					175	
		Cys	Leu	Ile	Asn 180	His	Leu	Val	Tyr	Val 185	Arg	Ile	Tyr	Gln	Ile 190	Ala	Lys
5		Arg	Arg	Thr 195	Arg	Val	Pro	Pro	Ser 200	Arg	Arg	Gly	Pro	Asp 205	Ala	Cys	Ser
		Ala	Pro 210	Pro	Gly	Gly	Ala	Asp 215	Arg	Arg	Pro	Asn	Ala 220	Val	Gly	Pro	Glu
		Arg 225	Gly	Ala	Gly	Thr	Ala 230	Gly	Gly	Gln	Gly	Glu 235	Glu	Arg	Ala	Gly	Gly 240
10		Ala	Lys	Ala	Ser	Arg 245	Trp	Arg	Gly	Arg	Gln 250	Asn	Arg	Glu	Lys	Arg 255	Phe
		Thr	Phe	Val	Ile 260	Ala	Val	Val	Ile	Gly 265	Val	Phe	Val	Val	Cys 270	Trp	Phe
15		Pro	Phe	Phe 275	Phe	Thr	Tyr	Thr	Leu 280	Ile	Ala	Val	Gly	Cys 285	Pro	Val	Pro
		Tyr	Gln 290	Leu	Phe	Asn	Phe	Phe 295	Phe	Trp	Phe	Gly	Tyr 300	Cys	Asn	Ser	Ser
		Leu 305	Asn	Pro	Val	Ile	Tyr 310	Thr	Ile	Phe	Asn	His 315	Asp	Phe	Arg	Arg	Ala 320
20		Phe	Lys	Lys	Ile	Leu 325	Cys	Arg	Gly	Asp	Arg 330	Lys	Arg	Ile	Val		
25	(2)		SEQ (A) (B) (C) (D)	UENC) LE) TY) ST	E CH NGTH PE: RAND POLO	SEQ ARAC : 32 amin EDNE GY: PE:	TERI 1 am 0 ac SS: line	STIC ino id sing ar	S: acid	s							
		(xi)	SEÇ	UENC	E DE	SCRI	PTIO	N: S	EQ I	D NO	:23:						
30		Leu 1	Leu	Thr	Ala	Leu 5	Val	Leu	Ser	Val	Ile 10	Ile	Val	Leu	Thr	Ile 15	Ile
		Gly	Asn	ılle	Leu 20	. Val	Ile	Leu	Ser	Val 25	. Phe	Thr	Туг	Lys	Pro 30	Leu	Arg
35		Ile	e Val	. Gln 35	Asr	n Phe	Phe	lle	Val	Ser	Ile	e Ala	. Val	Ala 45	Asp	Leu	Thr
		Val	Ala 50	ı Lev	ı Lev	ı Val	. Leu	Pro 55	Phe	Tr	Ala	а Туг	Ser 60	: Ile	e Leu	Gly	' Arg
		Trp 65	Glu	ı Phe	e Gly	/ Ile	His 70	: Leu	і Суя	s Lys	s Lev	75 75	Let	ı Thi	су Сув	Asp	Val 80
40		Let	ı Cys	s Cys	s Thi	s Ser 85	s Ser	r Ile	e Let	ı Ası	n Le v 90	ı Cys	s Ala	a Ile	e Ala	1 Le 1	ı Asp
											-			-			 ; .

Leu Ile Ser Ser Fro Pro Leu Ile Gly Trp Asn Asp Trp Pro Asp Glu

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		130					135					140				
	Phe 145	Thr	Ser	Ala	Thr	Pro 150	Cys	Glu	Leu	Thr	Ser 155	Gln	Arg	Ile	Gly	Tyr 160
5	Val	Ile	Tyr	Ser	Ser 165	Leu	Gly	Ser	Phe	Phe 170	Ile	Pro	Ile	Ala	Ile 175	Met
	Arg	Ile	Val	Tyr 180	Ile	Glu	Ile	Phe	Val 185	Ala	Thr	Arg	Arg	Arg 190	Leu	Arg
	Glu	Arg	Ala 195	Arg	Ala	Asn	Lys	Ile 200	Asn	Thr	Ile	Ala	Leu 205	Lys	Ser	Thr
10	Glu	Leu 210	Glu	Pro	Met	Ala	Asn 215	Ser	Ser	Pro	Val	Ala 220	Ala	Ser	Asn	Ser
	Gly 225	Ser	Lys	Lys	Lys	Thr 230	Ser	Gly	Val	Asn	Gln 235	Phe	Ile	Glu	Glu	Lys 240
15	Gln	Lys	Ile	Ser	Leu 245	Ser	Lys	Glu	Arg	Arg 250	Ala	Ala	Arg	Tha	Leu 255	Gly
	Ile	Ile	Met	Val 260	Fne	Val	Ile	Cys	Trp 265	Leu	Pro	Phe	Phe	Ile 270	Met	Tyr
	Val	Ile	Leu 275	Pro	Phe	Сув	Суѕ	Pro 280	Thr	Asn	Lys	Phe	Lys 285	Asn	Phe	Ile
20	Thr	Trp 290	Leu	Gly	Tyr	Ile	Asn 295	Ser	Gly	Leu	Asn	Pro 300	Val	Ile	Tyr	Thr
	Ile 305	Phe	Asn	Leu	Asp	Tyr 310	Arg	Arg	Ala	Phe	Lys 315	Arg	Leu	Leu	Gly	Leu 320
25	Asn															
	(2) INFO	TAMS	ON E	FOR S	SEQ I	D NO	0:24									
30		(A) (B) (C) (D)	JENCE LEN TYI STI	NGTH: PE: & RANDE POLOC	: 373 emino EDNES GY: 3	Bami aci SS: s linea	ino a id singl ar	cids	5							
	(ii) (xi)				_	-		O TT	NO.	. 24 .						
35			Leu								Leu	Ile	Leu	Ser	Thr 15	Leu
	Leu	Gly	Asn	Thr 20	Leu	Val	Cys	Ala	Ala 25	Val	Ile	Arg	Phe	Arg 30	His	Leu
	Arg	Ser	Lys 35	Val	Thr	Asn	Phe	Phe 40	Val	Ile	Ser	Leu	Ala 45	Val	Ser	Asp
40	Leu	Leu 50	Val	Ala	Val	Leu	Leu 55	Trp	Lys	Ala	Val	Ala 60	Glu	Ile	Ala	Gly
	Phe 65	Trp	Pro	Phe	Gly	Ser 70	Phe	Cys	Asn	Ile	Trp 75	Val	Ala	Phe	Asp	Ile 80
	Met	Cys	Ser	Thr	Ala	Ser	Ile	Leu	Asn	Leu	Cys	Val	Ile	Ser	Val	Asp
45		-			85					90	•				95	-

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					100					105					110		
		Pro	Lys	Ala 115	Ala	Phe	Ile	Leu	Ile 120	Ser	Val	Ala	Trp	Thr 125	Leu	Ser	Val
5		Leu	Ile 130	Ser	Phe	Ile	Pro	Val 135	Gln	Leu	Ser	Trp	His 140	Lys	Ala	Lys	Pro
		Thr 145	Ser	Pro	Ser	Asp	Gly 150	Met	Ala	Thr	Ser	Leu 155	Ala	Glu	Thr	Ile	Asp 160
		Asn	Cys	Asp	Ser	Ser 165	Leu	Ser	Arg	Thr	Tyr 170	Ala	Ile	Ser	Ser	Ser 175	Val
10		Ile	Ser	Phe	Tyr 180	Ile	Pro	Val	Ala	Ile 185	Leu	Val	Thr	Tyr	Thr 190	Arg	Ile
		Tyr	Arg	Ile 195	Ala	Gln	Lys	Gln	Ile 200	Arg	Arg	Ile	Ala	Ala 205	Leu	Glu	Arg
15		Ala	Ala 210	Val	His	Ala	Lys	Asn 215	Cys	Gln	Gly	Asn	Lys 220	Pro	Val	Glu	Cys
		Ser 225	Gln	Pro	Glu	Ser	Ser 230	Phe	Met	Ser	Phe	Lys 235	Arg	Glu	Thr	Lys	Val 240
		Leu	Lys	Thr	Leu	Ser 245	Val	Ile	Thr	Cys	Val 250	Phe	Val	Cys	Cys	Trp 255	Leu
20		Pro	Phe	Phe	Ile 260	Leu	Asn	Сув	Ile	Leu 265	Pro	Phe	Сув	Gly	Ser 270	Gly	Glu
		Thr	Gln	Pro 275	Phe	Сув	Thr	Asp	Ser 280	Asn	Thr	Phe	Asp	Val 285	Phe	Val	Trp
25		Phe	Gly 290	Trp	Ala	Asn	Ser	Ser 295	Leu	Asn	Pro	Ile	Ile 300	Tyr	Ala	Phe	Asn
		Ala 305	Asp	Phe	Arg	Lys	Ala 310	Phe	Ser	Thr	Leu	Leu 315	Gly	Cys	Tyr	Arg	Leu 320
		Cys	Pro	Ala	Thr	Asn 325	Met	Ala	Ile	Glu	Thr 330	Val	Ser	Ile	Asn	Asn 335	Gly
30		Ala	Ala	Met	Phe 340	Ser	Ser	His	His	Glu 345	Pro	Arg	Gly	Ser	Ile 350	Ser	Lys
		Glu	Сув	Asn 355	Leu	Val	Tyr	Leu	Ile 360		His	Ala	Val	Gly 365	Ser	Ser	Glu
35		Asp	Leu 370	Lys	Lys	Glu											
	(2)	INFO	SEQ	ION UENC) LE	E CH	ARAC	TERI	STIC	S :	ls							
40		1 x x 1	(B (C (D	TY	PE: RAND POLO	amin EDNE GY:	o ac SS: line	id sing ar									

Gly Asn Val Leu Val Cys Ala Ala Ile Val Arg Ser Arg His Leu Leu 20 25 30

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	Val	Phe	Ile 35	Val	Ser	Ile	Ala	Val 40	Ser	Asp	Leu	Phe	Val 45	Ala	Leu	Leu
	Val	Asn 50	Thr	Trp	Lys	Ala	Tyr 55	Ala	Glu	Val	Ala	Gly 60	Tyr	Trp	Pro	Phe
5	Gly 65	Ala	Phe	Cys	Asp	Val 70	Trp	Val	Ala	Phe	Asp 75	Ile	Met	Cys	Ser	Thr 80
	Ala	Ser	Ile	Leu	Asn 85	Leu	Сув	Val	Ile	Ser 90	Val	qaA	Arg	Tyr	Trp 95	Ala
10	Ile	Ser	Arg	Pro 100	Phe	Arg	Tyr	Lys	Ala 105	Leu	Val	Met	Val	Gl _y 110	Ile	Ala
	Trp	Thr	Leu 115	Ser	lle	Leu	Ile	Ser 120	Phe	Ile	Pro	Val	Gln 125	Ile	Asn	Trp
	Asn	Arg 130	Asp	Gln	Ala	Ala	Ser 135	Trp	Gly	Gly	Leu	Asp 140	Leu	Pro	Asn	Asn
15	Ile 145	Asp	Cys	qaA	Ser	Ser 150	Leu	Asn	Arg	Thr	Tyr 155	Ala	Ile	Ser	Ser	Ser 160
	Leu	Ile	Ser	Phe	Tyr 165	Ile	Pro	Val	Ala	Ile 170	Leu	Val	Thr	Tyr	Thr 175	Arg
20	Ile	Tyr	Arg	Ile 180	Ala	Gln	Val	Gln	Ile 185	Arg	Arg	Ile	Ser	Ser 190	Leu	Glu
	Arg	Ala	Ala 195	Glu	His	Ala	Gln	Ser 200	Cys	Arg	Ser	Ser	Ala 205	Ala	Cys	Ala
	Pro	Asp 210	Thr	Ser	Leu	Arg	Ala 215	Ser	Ile	Lys	Lys	Glu 220	Thr	Lys	Val	Leu
25	Lys 225	Thr	Leu	Ser	Val	11e 230	Ile	Cys	Val	Phe	Val 235	Cys	Cys	Trp	Leu	Pro 240
	Phe	Phe	Ile	Leu	Asn 245	Cys	Met	Val	Pro	Phe 250	Cys	Ser	Gly	Hij	Pro 255	Glu
30	Gly	Pro	Pro	Ala 260	Gly	Phe	Pro	Cys	Val 265	Ser	Glu	Thr	Thr	Phe 270	Asp	Val
	Phe	Val	Trp 275	Phe	Gly	Trp	Ala	Asn 280	Ser	Ser	Leu	Asn	Pro 285	Val	Ile	Tyr
	Ala	Phe 290	Asn	Ala	Asp	Phe	Gln 295	Lys	Val	Phe	Ala	Gln 300	Leu	Leu	Cys	Ser
35	His 305	Phe	Cys	Ser	Arg	Thr 310	Pro	Val	Glu	Thr	Val 315	Asn	Ile	Ser	Asn	Glu 320
	Leu	Ile	Ser	Tyr	Asn 325	Gln	Asp	Ile	Val	Phe 330	His	Lys	Glu	Ile	Ala 335	Ala
40	Ala	Tyr	Ile	His 340	Met	Met	Pro	Asn	Ala 345	Val	Thr	Pro	Gly	Asn 350	Arg	Glu
	Val	Asp	Asn 355	Asp	Glu	Glu	Glu	Gly 360								

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	(11)	MOLE	ECULE	TY	PE: F	pepti	Lde									
5	(xi) Tyr 1										Leu	Ile	Ala	Va.	Ile 15	Val
	Phe	Gly	Asn	Val 20	Leu	Val	Cys	Met	Ala 25	Val	Ser	Arg	Glu	Lys 30	Ala	Leu
10	Gln	Thr	Met 35	Asn	Tyr	Leu	Ile	Val 40	Ser	Ile	Ala	Val	Ala 45	Asp	Leu	Leu
	Val	Ala 50	Thr	Leu	Val	Trp	Trp 55	Trp	Tyr	Leu	Glu	Val 60	Val	Gly	Glu	Trp
	Lys 65	Phe	Ser	Arg	Ile	His 70	Cys	Asp	Ile	Phe	Val 75	Thr	Leu	Asp	Ile	Thr 80
L5	Ala	Ser	Ile	Leu	Asn 85	Leu	Cys	Ala	Ile	Ser 90	Ile	Asp	Arg	Tyr	Thr 95	Ala
	Val	Ala	Met	Pro 100	Met	Leu	Tyr	Asn	Thr 105	Arg	Tyr	Ser	Ser	Lys 110	Arg	Arg
20	Val	Thr	Val 115	Met	Ile	Ser	Ile	Val 120	Trp	Val	Leu	Ser	Phe 125	Thr	Ile	Ser
	Cys	Pro 130	Leu	Leu	Phe	Gly	Leu 135	Asn	Asn	Ala	Asp	Gln 140	Asn	Glu	Cys	Ile

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

- Glu Asp Met Lys Leu Cys Thr Val Ile Pro Asn Gly Lys Thr Arg Thr 210

 Ser Leu Lys Thr Met Ser Arg Arg Lys Leu Ser Gln Gln Lys Glu Lys 230

 Lys Ala Thr Gln Met Ile Ala Ile Val Leu Gly Val Phe Ile Ile Cys 255

 Lys Leu Pro Phe Phe Ile Thr His Ile Leu Asn Ile His Cys Asp Cys
- Asn Ile Pro Pro Val Leu Tyr Ser Ala Phe Thr Trp Leu Gly Tyr Val 275 280 285

Ash Ser Ala Val Ash Pro Tle Tie Tim Thr Thr Phe Ash Ile Glu Phe

Ile Ala Asn Pro Ala Phe Val Val Tyr Ser Ser Ile Val Se. Phe Tyr

Val Pro Phe Ile Val Thr Leu Leu Val Tyr Ile Lys Ile Tyr Ile Val

Leu Arg Arg Arg Lys Arg Val Asn Thr Lys Arg Ser Ser Arg Ala 180 185 190

Phe Arg Ala His Leu Arg Ala Pro Leu Lys Gly Asn Cys Thr His Pro

25

^{45 (2)} INFORMATION FOR SEQ ID NO:27: (i) SEQUENCE CHARACTERISTICS:

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5	(ii)	(B) (C) (D)	LEN TYP STF TOP ECULE	PE: 6 RANDI POLOC	mino EDNES EY:]	s aci SS: s linea	id singl ar		;							
	(xi) Ala 1		J EN CE Tyr								Ile	Leu	Ala	Ile	Val 15	Phe
10	Gly	Asn	Gly	Leu 20	Val	Cys	Met	Ala	Val 25	Leu	Arg	Glu	Lys	Ala 30	Leu	Gln
	Thr	Thr	Thr 35	Asn	Tyr	Leu	Val	Val 40	Ser	Leu	Ala	Val	Ala 45	Asp	Leu	Leu
	Val	Ala 50	Thr	Leu	Val	Trp	Trp 55	Val	Val	Tyr	Leu	Glu 60	Val	Thr	Gly	Gly
15	Val 65	Trp	Asn	Phe	Ser	Arg 70	Ile	Cys	Cys	Asp	Val 75	Phe	Val	Thr	Leu	Asp 80
	Val	Met	Met	Thr	Ala 85	Ser	Ile	Leu	Asn	Leu 90	Cys	Ala	Ile	Ser	Ile 95	qaA
20	Arg	Tyr	Thr	Ala 100	Val	His	Tyr	Gln	His 105	Gly	Thr	Gly	Gln	Ser 110	Ser	Cys
	Arg	Arg	Val 115	Ala	Ile	Met	Ile	Thr 120	Ala	Val	Trp	Val	Leu 125	Ala	Phe	Ala
	Val	Ser 130	Cys	Pro	Leu	Leu	Phe 135	Gly	Phe	Asn	Thr	Gly 1 4 0	Asp	Pro	Thr	Val
25	Cys 145	Ser	Ile	Ser	Asn	Pro 150	qaA	Phe	Val	Ile	Tyr 155	Ser	Ser	Val	Val	Ser 160
	Phe	Tyr	Leu	Pro	Phe 165	Gly	Val	Thr	Val	Leu 170	Val	Tyr	Ala	Arg	Ile 175	Tyr
30	Val	Val	Leu	Lys 180	Gln	Arg	Arg	Arg	Lys 185	Arg	Ile	Leu	Thr	Arg 190	Gln	Asn
	Ser	Gln	Cys 195	Asn	Ser	Val	Arg	Pro 200	Gly	Phe	Pro	Gln	Gln 205	Ser	Thr	Ser
	Leu	Pro 210	Asp	Pro	Ala	His	Leu 215	Glu	Leu	Lys	Arg	Ser 220	Asn	Gly	Arg	Leu
35	Ser 225	Thr	Ser	Leu	Lys	Leu 230	Pro	Leu	Gln	Pro	Arg 235	Gly	Val	Pro	Leu	Arg 240
	Glu	Lys	Lys	Ala	Thr 245	Gln	Met	Val	Ala	Ile 250	Val	Leu	Gly	Ala	Phe 255	Ile
40	Val	Cys	Trp	Leu 260		Phe	Phe	Leu	Thr 265	His	Val	Ile	Asn	Thr 270	His	Cys
	Gln	Thr	Cys 275	His	Val	Ser	Pro	Glu 280	Leu	Tyr	Ser	Ala	Thr 285	Thr	Trp	Leu
	Gly	Tyr 290	Val	Asn	Ser	Ala	Leu 295		Pro	Val	Ile	Tyr 300		Thr	Phe	Asn
45	Ile 305		Phe	Arg	Lys	Ala 310		Leu	Lys	Ile	Leu 315	Ser	Cys			

(2) INFORMATION FOR SEQ ID NO:28:

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5	(i) (ii)	(A) (B) (C) (D)	ENCE LEN TYP STR TOP	GTH: E: a ANDE OLOG	315 minc DNES Y: 1	ami aci S: s inea	no a .d singl ir	cids	:							
LO	(xi) Gly 1	SEQU Ala	ENCE Ala	DES Ala	CRIP Leu 5	TION Val	I: SE Gly	Q ID Gly	NO: Val	28: Leu 10	Leu	Ile	Cys	Ala	Val 15	Leu
	Ala	Gly	Asn	Ser 20	Leu	Val	Cys	Val	Ser 25	Val	Ala	Thr	Glu	Arg 30	Ala	Leu
	Gln	Thr	Pro 35	Thr	Asn	Ser	Phe	Ile 40	Val	Ser	Leu	Ala	Ala 45	Ala	qaA	Leu
15	Leu	Leu 50	Ala	Leu	Leu	Val	Leu 55	Pro	Leu	Phe	Val	Tyr 60	Ser	Glu	Val	Gln
	Gly 65	Ala	Ala	Trp	Leu	Leu 70	Ser	Pro	Arg	Leu	Cys 75	Asp	Val	Met	Leu	Cys 80
20	Thr	Ala	Ser	Ile	Phe 85	Asn	Leu	Сув	Ala	Ile 90	Ser	Val	Asp	Ar	Phe 95	Val
	Ala	Val	Ala	Val 100	Pro	Leu	Arg	Tyr	Asn 105	Arg	Gln	Gly	Gly	Ser 110	Arg	Arg
	Gln	Leu	Leu 115	Leu	Ile	Gly	Ala	Thr 120	Trp	Leu	Leu	Ser	Ala 125	Ala	Val	Ala
25	Ala	Pro 130	Val	Leu	Cys	Gly	Leu 135	Asn	Asp	Val	Arg	Gly 140	Arg	Asp	Pro	Ala
	Val 145	Cys	Arg	Leu	Glu	Asp 150	Arg	qaA	Tyr	Val	Val 155	Tyr	Ser	Ser	Val	Cys 160
30	Ser	Phe	Phe	Leu	Pro 165	Cys	Pro	Leu	Leu	Tyr 170	Trp	Ala	Thr	Phe	Arg 175	Gly
	Leu	Gln	Leu	Val 180	Ala	Arg	Arg	Ala	Lys 185		His	Gly	Arg	Ala 190	Pro	Arg
	Arg	Pro	Ser 195	Gly	Pro	Gly	Pro	Pro 200	Ser	Pro	Thr	Pro	Pro 205	Ala	Pro	Arg
35	Leu	Pro 210	Gln	Asp	Pro	Cys	Gly 215		Leu	Pro	Pro	Gln 220	Thr	Pro	Pro	Gln
	Thr 225		Arg	Arg	Arg	Arg 230		Lys	Ile	Thr	Gly 235		Glu	Arg	Lys	Ala 240
40	Met	Arg	Val	Leu	Pro 245		Val	Val	Gly	Ala 250		Ile	Leu	Cys	Trp 255	
	Pro	Phe	Phe	Val 260		His	Ile	Thr	Gln 265		Leu	Cys	Pro	Ala 270		Ser

Asn Val Phe Arg Lys Ala Leu Arg Ala Cys Cys

Bornell Control of the MATE

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(2) INFORMATION FOR SEQ ID NO:29: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 327 amino acids 5 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29: 10 Lys Ile Ser Leu Ala Val Val Leu Ser Val Ile Thr Leu Ala Thr Val Leu Ser Asn Ala Phe Val Leu Thr Arg Ile Leu Leu Thr Arg Lys Leu His Thr Pro Ala Asn Tyr Leu Ile Gly Ser Ile Ala Thr Thr Asp Leu 15 Leu Val Ser Ile Leu Val Trp Ile Ser Ile Ala Tyr Thr Ile Thr His Thr Trp Asn Phe Gly Gln Ile Leu Cys Asp Ile Trp Leu Ser Ser Asp 20 Ile Thr Cys Cys Thr Ala Ser Ile Leu His Leu Cys Val Ile Ala Leu Asp Arg Tyr Trp Ala Ile Thr Asp Ala Leu Glu Tyr Ser Lys Arg Arg Thr Ala Gly His Ala Ala Thr Met Ile Ala Ile Val Trp Ala Ile Ser 25 Ile Cys Ile Ser Ile Pro Pro Leu Phe Trp Arg Ala Lys Ala Gln Glu Glu Met Ser Asp Cys Leu Val Asn Thr Ser Gln Ser Tyr Thr Ile Tyr 155 30 Ser Thr Cys Gly Ala Phe Tyr Ile Pro Ser Val Leu Leu Ile Ile Leu Tyr Gly Arg Ile Tyr Arg Ala Ala Arg Asn Arg Ile Leu Asn Pro Pro Ser Leu Tyr Gly Lys Arg Phe Thr Thr Ala His Leu Ile Thr Gly Ser 35 200 Ala Gly Ser Ser Leu Cys Ser Leu Asn Ser Ser Leu His Glu Gly His Asn His Val Lys Ile Lys Leu Ala Asp Ser Ala Leu Glu Arg Lys Arg 40 Ile Ser Ala Ala Arg Glu Arg Lys Ala Thr Lys Ile Leu Gly Ile Ile Leu Gly Ala Phe Ile Ile Cys Trp Leu Pro Phe Phe Val Val Ser Leu 265 Val Leu Pro Ile Cys Arg Asp Ser Cys Trp Ile His Pro Ala Leu Phe 45 Asp Phe Phe Thr Trp Leu Gly Tyr Ile Asn Ser Leu Ile Asn Pro Ile 295 300

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Ile Tyr Thr Val Phe Asn Glu Glu Phe Arg Gln Ala Phe Gln Lys Ile

Val Pro Phe Arg Lys Ala Ser 325 (2) INFORMATION FOR SEQ ID NO:30: (i) SEOUENCE CHARACTERISTICS: (A) LENGTH: 325 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single
(D) TOPOLOGY: linear 10 (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30: Val Ile Thr Ser Leu Leu Gly Thr Leu Ile Phe Cys Ala Val Leu Gly Asn Ala Cys Val Val Ala Ala Ile Ala Leu Glu Arg Ser Leu Gln 15 Asn Val Ala Asn Tyr Leu Ile Gly Ser Leu Ala Val Arg Asp Leu Met Val Ser Val Leu Val Leu Pro Met Ala Ala Leu Tyr Gln Val Leu Asn 20 Lys Trp Thr Leu Gly Gln Val Thr Cys Asp Leu Phe Ile Ala Leu Asp Val Leu Cys Cys Thr Ser Ser Ile Leu His Leu Cys Ala Ile Ala Leu Asp Arg Tyr Trp Ala Ile Thr Asp Pro Ile Asp Tyr Val As: Lys Arg 25 105 Thr Pro Arg Pro Arg Ala Leu Ile Ser Leu Thr Trp Leu Ile Gly Phe 120 Leu Ile Ser Ile Pro Pro Met Leu Gly Trp Arg Thr Pro Glu Asp Arg 30 Ser Asp Pro Asp Ala Cys Thr Ile Ser Lys Asp His Gly Tyr Thr Ile Tyr Ser Thr Ile Phe Ala Phe Tyr Ile Pro Leu Leu Met Leu Val Leu Tyr Gly Arg Ile Phe Arg Ala Ala Arg Phe Arg Ile Arg Lys Thr 35 Val Lys Lys Val Glu Lys Thr Gly Ala Asp Thr Arg His Gly Ala Ser 200 Pro Ala Pro Gln Pro Lys Lys Ser Val Asn Gly Glu Ser Gly Ser Arg 40 Asn Ala Ser Phe Glu Arg Lys Asn Glu Arg Asn Ala Phe Ala Lys Leu 235 230

Phe Cys Glu Ser Ser Cys His Met Pro Thr Leu Ile Arg Ala Ile Ile

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			275					280					285			
	Asn	Trp 290	Leu	Cys	Val	Ile	Asn 295	Ser	Leu	Leu	Asn	Pro 300	Val	Ile	Tyr	Ala
5	Tyr 305	Phe	Asn	Lys	Asp	Phe 310	Gln	Asn	Ala	Phe	Lys 315	Lys	Ile	Ile	Lys	Cys 320
	Asn	Phe	Cys	Arg	Gln 325											
10	(2) INFOR	SEQU (A) (B) (C) (D)	JENCE LEN TYI STI TOI	CHANDE: 6	RACT 385 mino DNES SY: 1	ERIS ami aci SS: s inea	STICS ino a id singl	: cids	5							
15	(xi) Gln 1	SEQU Asn									Ile	Ile	Ile	Asn	Thr 15	Ile
	Gly	Gly	Asn	Ile 20	Leu	Val	Ile	Met	Ala 25	Val	Ser	Lys	Lys	Leu 30	His	Asn
20	Ala	Thr	Asn 35	Tyr	Phe	Leu	Met	Ser 40	Ile	Ala	Ile	Ala	Asp 45	Me	Leu	Val
	Gly	Phe 50	Leu	Val	Trp	Leu	Ser 55	Leu	Leu	Ala	Ile	Leu 60	Tyr	Asp	Tyr	Val
25	Trp 65	Pro	Leu	Pro	Arg	Tyr 70	Leu	Cys	Pro	Val	Trp 75	Ile	Ser	Leu	Asp	Val 80
	Leu	Phe	Ser	Thr	Ala 85	Ser	Ile	Met	His	Leu 90	Сув	Ala	Ile	Ser	Leu 95	Asp
	Arg	Tyr	Val	Ala 100	Ile	Arg	Asn	Pro	Ile 105	Glu	His	Ser	Arg	Phe 110	Ser	Arg
30	Thr	Lys	Ala 115	Ile	Met	Lys	Ile	Ala 120	Ile	Val	Trp	Ala	Ile 125	Ser	Ile	Gly
	Val	Ser 130	Val	Pro	Ile	Pro	Val 135	Ile	Gly	Leu	Arg	Asp 140	Glu	Ser	Lys	Val
35	Phe 145	Val	Asn	Asn	Thr	Thr 150	Ile	Cys	Val	Leu	As n 155	Asp	Pro	Asn	Phe	Val 160
	Leu	Ile	Gly	Ser	Phe 165	Val	Ala	Phe	Phe	Ile 170	Pro	Thr	Leu	Ile	Met 175	Val
	Ile	Thr	Tyr	Phe 180	Leu	Thr	Ile	Tyr	Val 185	Leu	Arg	Arg	Gln	Th. 190	Leu	Met
40	Leu	Leu	Arg 195	Gly	His	Thr	Glu	Glu 200	Glu	Ile	Ala	Met	Ser 205	Leu	Asn	Phe
	Leu	Asn 210	Cys	Cys	Cys	Lys	Lys 215	Asn	Gly	Gly	Glu	Glu 220	Glu	Asn	Ala	Pro
45	Asn 225	Asn	Pro	Asn	Pro	Asp 230	Gln	Lys	Pro	Arg	Arg 235	Lys	Lys	Lys	Glu	Lys 240
	Arg	Pro	Arg	Gly	Thr 245	Met	Gln	Ala	Ile	Asn 250	Asn	Glu	Lys	Lys	Ala 255	Ser

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		Lys	Val	Leu	Gly 260	Ile	Val	Phe	Phe	Val 265	Phe	Leu	Ile	Met	Tro 270	Cys	Pro
		Phe	Phe	Ile 275	Thr	Asn	Ile	Leu	Ser 280	Val	Leu	Cys	Gly	Lys 285	Ala	Cys	Asn
5		Gln	Cys 290	Lys	Leu	Leu	Asn	Val 295	Phe	Val	Trp	Ile	Gly 300	Tyr	Val	Cys	Ser
		Gly 305	Ile	Asn	Pro	Val	Ile 310	Tyr	Thr	Leu	Phe	Asn 315	Lys	Ile	Tyr	Arg	Arg 320
10		Ala	Phe	Ser	Lys	Tyr 325	Leu	Arg	Cys	Asp	Tyr 330	Lys	Pro	Asp	Lys	Lys 335	Pro
		Pro	Val	Arg	Gln 340	Ile	Pro	Arg	Val	Ala 345	Ala	Thr	Ala	Leu	Ser 350	Gly	Arg
		Glu	Leu	Asn 355	Val	Asn	Ile	Tyr	Arg 360	His	Thr	naA	Glu	Arg 365	Val	Ala	Arg
15		Lys	Ala 370	Asn	qaA	Pro	Glu	Pro 375	Gly	Ile	Glu	Asn	Gln 380	Val	Glu	Asn	Leu
		Glu 385															
20	(2)		SEQUAL (A)	JENCE LEN	CHA	ARAC:	reris	STICS ino a	3:	5							
25		(ii)	(C)) STI	RANDI	EDNES	SS: :	sing. ar	le								
25		(xi)	(C) (D) MOLI) STI	RANDI POLOC E TYI	EDNES SY: : PE: :	SS: s linea pept: PTIO	sing: ar ide N: SI	EQ II			Val	Ile	Ile	Leu	Thr 15	Ile
25 30		(xi) Lys 1	(C) (D) MOLI SEQI Asn) STI) TOI ECULI UENCI	RANDI POLOC E TYI E DES	EDNES SY: SPE: 1 SCRII Ala 5	SS: s linea pept: PTIOI Leu	sing: ar ide N: SI Leu	€Q II Thr	Thr	Val 10					15	
		(xi) Lys 1 Ala	(C) (D) MOLI SEQUASE) STI) TOI ECULI UENCI Trp	RANDI POLOG E TYI E DES Ser Ile 20	EDNES GY: : PE: : I SCRII Ala 5	SS: slines pept: PTIOI Leu Val	sing: ar ide N: SI Leu	SQ II Thr Met	Thr Ala 25	Val 10 Val	Ser	Leu	Glu	Lys 30	15 Lys	Leu
		(xi) Lys 1 Ala Gln	(C) (D) MOLI SEQN Asn Gly) STE) TOE ECULE UENCE Trp Asn Ala 35	RANDI POLOX E TYI E DES Ser Ile 20 Thr	EDNES GY: : PE: : SCRII Ala 5 Leu Asn	SS: flineacept: PTION Leu Val	singlar ide N: SI Leu Ile	EQ II Thr Met Leu 40	Thr Ala 25 Met	Val 10 Val Ser	Ser	Leu Ala	Glu Ile 45	Lys 30 Ala	Lys Asp	Leu
		(xi) Lys 1 Ala Gln Leu	(C: (D) MOLD SEQUENT Asn Gly Asn Leu 50) STE) TOE ECULE UENCE Trp Asn Ala 35	E DES Ser Ile 20 Thr	EDNES SY: SPE: PE: PE: PE: PE: PE: PE: PE: PE: PE:	SS: flineapept: PTION Leu Val Tyr Val	singlar ide N: SI Leu Ile Phe Trp 55	Thr Met Leu 40	Thr Ala 25 Met	Val 10 Val Ser Asn	Ser Leu Glu	Leu Ala Thr	Glu Ile 45 Ile	Lys 30 Ala Leu	Lys Asp Tyr	Leu Met Gly
30		(xi) Lys 1 Ala Gln Leu Tyr 65	(C: (D) MOLD SEQUENT Asn Gly Asn Leu 50 Arg) STH) TOB ECULH UENCH Trp Asn Ala 35	E DES Ser Ile 20 Thr Phe	EDNES SY: SPE: PE: PE: PE: PE: PE: PE: PE: PE: PE:	SS: flineapept: PTION Leu Val Tyr Val Pro 70	singlar ide N: SI Leu Ile Phe Trp 55 Ser	EQ II Thr Met Leu 40 Val	Thr Ala 25 Met Ser Leu	Val 10 Val Ser Asn Cys	Ser Leu Glu Ala 75	Leu Ala Thr 60	Glu Ile 45 Ile Trp	Lys 30 Ala Leu	Lys Asp Tyr	Leu Met Gly Leu 80
30		(xi) Lys 1 Ala Gln Leu Tyr 65 Asp	(C) (D) MOLI SEQUASI Gly Asin Leu 50 Arg) STH) TOH ECULH UENCH Trp Asn Ala 35 Gly	E DES Ser Ile 20 Thr Phe Pro	EDNES SY: SPE: I SCRII Ala 5 Leu Asn Leu Leu Ser 85	SS: Slinea pept: PTION Leu Val Tyr Val Pro 70 Thr	sing: ar ide N: SI Leu Ile Phe Trp 55 Ser Ala	Met Leu 40 Val Lys	Thr Ala 25 Met Ser Leu Ile	Val 10 Val Ser Asn Cys Met 90 Pro	Ser Leu Glu Ala 75 His	Leu Ala Thr 60 Ile	Glu Ile 45 Ile Trp Cys	Lys 30 Ala Leu Ile	Lys Asp Tyr Tyr Arg	Leu Met Gly Leu 80 Ser
30		(xi) Lys 1 Ala Gln Leu Tyr 65 Asp	(C) (D) MOLD SEQUENCE As n SEQ) STH) TOH ECULH UENCH Trp Asn Ala 35 Gly Trp Leu	E DES Ser Ile 20 Thr Phe Pro	EDNES SY: SY: SPE: N SCRIN Ala 5 Leu Asn Leu Leu Ser 85 Val	SS: flineapept: PTION Leu Val Tyr Val Pro 70 Thr	sing: ar ide N: SI Leu Ile Phe Trp 55 Ser Ala Ile	Met Leu 40 Val Lys Ser	Thr Ala 25 Met Ser Leu Ile Asn 105 Lys	Val 10 Val Ser Asn Cys Met 90 Pro	Ser Leu Glu Ala 75 His	Leu Ala Thr 60 Ile Leu His	Glu Ile 45 Ile Trp Cys	Lys 30 Ala Leu Ile Ala Ser 110	Lys Asp Tyr Tyr Ile 95 Arg	Leu Met Gly Leu 80 Ser

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		Val	Leu	Ile	Gly	Ser 165	Phe	Val	Ala	Phe	Phe 170	Ile	Pro	Leu	Thr	Ile 175	Met
		Val	Ile	Thr	Tyr 180	Phe	Leu	Thr	Ile	Lys 185	Ser	Leu	Arg	Gln	Lys 190	Phe	Ala
5		Thr	Leu	Cys 195	Val	Ser	Asp	Leu	Ser 200	Thr	Arg	Ala	Lys	Leu 205	Ala	Ser	Phe
		Ser	Phe 210	Leu	Pro	Gln	Ser	Ser 215	Leu	Ser	Ser	Glu	Lys 220	Leu	Phe	Gln	Arg
10		Ser 225	Ile	His	Arg	Glu	Pro 230	Gly	Ser	Tyr	Ala	Gly 235	Arg	Lys	Thr	Met	Gln 240
		Ser	Ile	Ser	Asn	Glu 245	Gln	Lys	Ala	Cys	Lys 250	Val	Leu	Gly	Ile	Val 255	Phe
		Phe	Leu	Phe	Val 260	Val	Met	Trp	Cys	Pro 265	Phe	Phe	Ile	Thr	Asn 270	Ile	Met
15		Val	Ile	Cys 275	Lys	Glu	Ser	Cys	Asn 280	Glu	Asn	Val	Ile	Gly 285	Ala	Leu	Leu
		Asn	Val 290	Phe	Val	Trp	Ile	Gly 295	Tyr	Leu	Ser	Ser	Ala 300	Val	Asn	Pro	Leu
20		Val 305	Tyr	Thr	Leu	Phe	Asn 310	Lys	Thr	Tyr	Arg	Ser 315	Ala	Phe	Ser	Arg	Tyr 320
		Leu	Gln	Cys	Gln	Tyr 325	Lys	Glu	Asn	Arg	Lys 330	Pro	Leu	Leu	Ile	Leu 335	Val
		Asn	Thr	Ile	Pro 340	Ala	Leu	Ala	Tyr	Lys 345	Ser	Ser	Gln	Leu	Gln 350	Val	Gly
25		Gln	Lys	Lys 355	Asn	Ser	Gln	Glu	Asp 360	Ala	Glu	Gln	Thr	Val 365	ĄsĄ	Asp	Cys
		Ser	Me t 370	Val	Thr	Leu	Gly	Lys 375	Gln	Gln	Ser	Glu					
30	(2)		SEQI (A (B (C	UENC:) LE:) TY:	E CHI NGTH PE: 8 RAND	ARAC' : 33' emino EDNE!	reri: 7 am: 5 ac: 5S:	STIC: ino a id sing:	S: acid:	5							
35				ECUL:													
				UENC: Ile								Ile	Leu	Ile	Thr	Val 15	Ala
40		Gly	Asn	Val	Val 20	Val	Cys	Ile	Ala	Val 25	Gly	Ile	Asn	Arg	Arg 30	Leu	Arg
		Asn	Leu	Thr 35	Asn	Cys	Phe	Ile	Val 40	Ser	Leu	Ala	Ile	Thr 45	Asp	Leu	Leu
		Leu	Gly 50	Leu	Leu	Val	Leu	Pro 55	Phe	Ser	Ala	Ile	Tyr 60	Gln	Leu	Ser	Cys
45		Lys 65	Trp	Ser	Phe	Gly	Lys 70	Val	Phe	Cys	Asn	Ile 75	Tyr	Thr	S€r	Leu	Asp 80
		Val	Met	Leu	Cys	Thr	Ala	Ser	Ile	Leu	Asn	Leu	Leu	Ile	Ser	Leu	Asp

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			85				90					95	
	Arg Ty	r Cys Al		Met Asp	Pro	Leu 105	Arg	Tyr	Pro	Val	Leu 110	Val	Arg
5	Pro Va	l Arg Va 115	l Ala I	Ile Ser	Leu 120	Val	Leu	Ile	Trp	Val 125	Ile	Ser	Ile
	Thr Le	u Ser Pho	e Leu S	Ser Ile 135		Leu	Gly	Trp	Asn 140	Ser	Arg	Asn	Glu
	Thr Se 145	r Lys Gl		His Thr 150	Thr	Ser	Lys	Cys 155	Lys	Val	Gln	Val	Asn 160
10	Glu Va	l Tyr Gl	/ Leu \ 165	Val Asp	Gly	Leu	Val 170	Thr	Phe	Tyr	Leu	Pro 175	Leu
	Leu Il	e Met Cya 18		Thr Tyr	Tyr	Arg 185	Ile	Phe	Lys	Val	Ala 190	Arg	Asp
15	Ala Ly	s Arg Ası 195	His I	Ile Ser	Ser 200	Trp	Lys	Ala	Ala	Thr 205	Ile	Arg	Glu
	His Ly	s Ala Th:)	r val u	Thr Ile 215	Ala	Ala	Val	Met	Ala 220	Phe	Ile	Ile	Cys
	Trp Pho 225	Pro Ty		Thr Ala 230	Phe	Val	Tyr	Arg 235	Gly	Leu	Arg	Gly	Asp 240
20	Asp Ala	a Ile Ası	Glu V 245	Val Leu	Glu	Ala	Ile 250	Val	Leu	Trp	Leu	Gly 255	Tyr
	Ala As	n Ser Ala 260		Asn Pro	Ile	Leu 265	Tyr	Ala	Ala	Leu	Asn 270	Arg	Asp
25	Phe Ar	g Thr Gly 275	Tyr C	Gln Gln	Leu 280	Phe	Cys	Cys	Arg	Ile 285	Ala	Asn	Arg
	Asn Se	r His Ly	Thr S	Ser Leu 295	Arg	Ser	Asn	Ala	Ser 300	Gln	Leu	Ser	Arg
	Thr Gla	n Ser Arg		Pro Arg 310	Gln	Gln	Glu	Glu 315	Lys	Pro	Leu	Lys	Leu 320
30	Gln Va	l Trp Se	Gly 1 325	Thr Glu	Val	Thr	Ala 330	Pro	Gln	Gly	Ala	Thr 335	qaA
	Arg												

- (2) INFORMATION FOR SEQ ID NO:34:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 315 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single

 - (D) TOPOLOGY: linear
- 40 (ii) MOLECULE TYPE: peptide

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Val Thr Thr Ile Ser Tyr Leu Asn Leu Ala Val Ala Asp Phe Cys Phe

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35 40 45 Thr Ser Thr Leu Pro Phe Phe Met Val Arg Leu Gly His Trp Pro Phe Gly Trp Phe Leu Cys Lys Phe Leu Phe Thr Ile Val Asp Ile Asn Leu Phe Gly Ser Val Phe Leu Ile Ala Leu Ile Ala Leu Asp Arg Cys Val Cys Val Leu His Pro Val Trp Thr Gln Asn His Arg Thr Val Ser Leu 10 Ala Lys Lys Val Ile Ile Gly Pro Trp Val Met Ala Leu Leu Thr 120 Leu Pro Val Ile Ile Arg Val Thr Ile Val Pro Gly Lys Thr Gly Thr Val Ala Cys Thr Phe Asn Phe Ser Pro Trp Thr Asn Asp Pro Lys Glu 15 150 155 Arg Ile Asn Val Ala Val Ala Met Leu Thr Val Arg Gly Ile Ile Arg Phe Ile Ile Gly Phe Ser Ala Pro Met Ser Ile Val Ala Val Ser Tyr 185 20 Gly Leu Ile Ala Thr Lys Ile Ile Lys Ser Ser Arg Pro Leu Arg Val Leu Ser Phe Val Ala Ala Ala Phe Phe Leu Cys Trp Ser Pro Tyr Gln Val Val Ala Leu Ile Ala Thr Val Arg Ile Arg Glu Leu Leu Gln Gly 25 Met Tyr Lys Glu Ile Gly Ile Ala Val Asp Val Thr Ser Ala Ile Ala Phe Phe Asn Ser Cys Leu Asn Pro Leu Tyr Val Phe Met Gly Gln Asp 30 Phe Arg Glu Arg Leu Ile His Ala Leu Pro Ala Ser Leu Glu Arg Ala 280 Leu Thr Glu Asp Ser Thr Gln Thr Ser Asp Thr Ala Thr Asn Ser Thr 295 Leu Pro Ser Ala Glu Val Ala Leu Gln Ala Lys 35 310 (2) INFORMATION FOR SEQ ID NO:35: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 304 amino acids (B) TYPE: amino acid 40 (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35: Asp Ile Leu Ala Leu Val Ile Phe Ala Val Val Phe Leu Val Gly Val 45 Leu Gly Asn Ala Leu Val Val Trp Val Thr Ala Phe Glu Ala Lys Arg - 89 -

				20					25					30		
	Thr	Ile	Asn 35	Ala	Ile	Trp	Phe	Leu 40	Asn	Ile	Ala	Val	Ala 45	Asp	Phe	Leu
5	Ser	Cys 50	Leu	Ala	Leu	Pro	Ile 55	Leu	Phe	Thr	Ser	Ile 60	Val	Gln	His	His
	His 65	Trp	Pro	Phe	Gly	Gly 70	Ala	Ala	Cys	Ser	Ile 75	Leu	Pro	Ser	Leu	Ile 80
	Leu	Leu	Asn	Met	Tyr 85	Ala	Ser	Ile	Leu	Leu 90	Leu	Ala	Thr	Ile	Ser 95	Ala
10	Asp	Arg	Phe	Leu 100	Leu	Val	Phe	Lys	Pro 105	Ile	Trp	Cys	Gln	Asn 110	Phe	Arg
	Gly	Ala	Gly 115	Leu	Ala	Trp	Ile	Ala 120	Cys	Ala	Val	Ala	Trp 125	Gly	Ile	Ala
15	Leu	Leu 130	Leu	Thr	Ile	Pro	Ser 135	Phe	Leu	Tyr	Arg	Val 140	Val	Arg	Glu	Glu
	Tyr 145	Phe	Pro	Pro	Lys	Val 150	Leu	Cys	Gly	Cys	Asp 155	Tyr	Ser	His	Asp	Lys 160
	Arg	Arg	Glu	Arg	Ala 165	Val	Ala	Ile	Val	Arg 170	Leu	Val	Leu	Gly	Phe 175	Leu
20	Trp	Pro	Leu	Leu 180	Thr	Leu	Thr	Ile	Cys 185	Tyr	Thr	Thr	Arg	Ser 190	Thr	Lys
	Thr	Leu	Lys 195	Val	Val	Val	Ala	Val 200	Val	Ala	Ser	Phe	Phe 205	Ile	Phe	Trp
25	Leu	Pro 210	Tyr	Gln	Val	Thr	Gly 215	Ile	Met	Met	Ser	Phe 220	Leu	Glu	Pro	Ser
	Ser 225	Pro	Thr	Phe	Leu	Leu 230	Leu	Asn	Lys	Leu	Asp 235	Ser	Leu	Cys	Val	Ser 240
	Phe	Ala	Tyr	Ile	Asn 245	Cys	Сув	Ile	Asn	Pro 250	Ile	Ile	Tyr	Val	Val 255	Ala
30	Gly	Gln	Gly	Gln 260	Phe	Gln	Gly	Arg	Leu 265	Arg	Lys	Ser	Leu	Pro 270	Ser	Leu
	Leu	Arg	Asn 275	Val	Leu	Thr	Glu	Glu 280	Ser	Val	Val	Arg	Glu 285	Sei	Lys	Ser
35	Phe	Thr 290	Arg	Ser	Thr	Val	Asp 295		Met	Ala	Gln	Lys 300	Thr	Gln	Ala	Val

(2) INFORMATION FOR SEQ ID NO:36:

40

BASE SALE AND ARREST

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 322 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

Pro Leu Asn Ile Met Ala Ile Val Val Phe Ile Leu Lys Met Lys Val

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20 25 30 Lys Lys Pro Ala Val His Ile Ala Thr Ala Asp Val Leu Phe Val Ser Val Leu Pro Phe Lys Ile Ser Tyr Tyr Phe Ser Gly Ser Asp Trp Gln 5 Phe Gly Ser Glu Leu Cys Arg Phe Val Thr Ala Ala Phe Tyr Cys Asn Met Tyr Ala Ser Ile Leu Leu Ile Ser Ile Asp Arg Phe Ile Ala Val 10 Val Tyr Pro Met Gln Ser Leu Ser Trp Arg Thr Leu Gly Arg Ala Ser 105 Phe Thr Cys Ile Ala Ile Trp Ala Ile Ala Ile Ala Gly Val Pro Leu 120 Val Leu Lys Glu Gln Thr Ile Gln Val Pro Gly Leu Asn Ile Thr Thr 15 135 Ile Cys His Asp Val Leu Asn Glu Thr Leu Leu Glu Gly Tyr Tyr Ala 145 150 Tyr Tyr Phe Ser Ala Phe Ser Ala Val Phe Phe Val Pro Leu Ile 20 Ile Ser Thr Val Cys Tyr Val Ser Ile Ile Arg Cys Leu Ser Ser Ser 180 185 Ala Val Ala Asn Arg Ser Lys Lys Ser Arg Thr Asn Arg Cys Phe Asn Ser Thr Val Ala Leu Phe Leu Ser Ala Ala Val Phe Cys Ile Phe Ile 25 Ile Cys Phe Gly Pro Thr Trp Leu Leu Ile Ala His Tyr Ser Phe Leu Ser His Thr Ser Thr Thr Glu Ala Ala Tyr Phe Ala Tyr Leu Leu Cys 30 Val Cys Val Ser Ser Ile Ser Ser Cys Ile Asp Pro Leu Ile Tyr Tyr Tyr Ala Ser Ser Glu Cys Gln Arg Tyr Val Tyr Ser Ile Leu Cys Cys Lys Glu Ser Ser Asp Pro Ser Ser Tyr Asn Ser Ser Gly Gln Leu Met 35 Ser Leu Thr Cys Ser Ser Asn Leu Asn Asn Ser Ile Tyr Lys Lys Leu 305 310 Leu Thr 40 (2) INFORMATION FOR SEQ ID NO:37: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 311 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

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	(xi) Tyr 1	SEQU Ile	ENCE Asn	DES Thr	CRIF Val 5	TION Ile	I: SE Ser	Q II Cys	NO:	37: Ile 10	Phe	Ile	Val	Gly	Trp 15	Gly
5	Asn	Ala	Thr	Leu 20	Leu	Arg	Ile	Ile	Tyr 25	Gln	Asn	Lys	Cys	Met 30	Arg	Asn
	Gly	Pro	Asn 35	Ala	Leu	Ile	Ala	Ser 40	Ile	Ala	Leu	Gly	Asp 45	Leu	Ile	Tyr
	Val	Val 50	Ile	qaA	Leu	Pro	Ile 55	Asn	Val	Pro	Lys	Leu 60	Ile	Ala	Gly	Arg
10	Trp 65	Pro	Phe	Glu	Gln	Asn 70	Asp	Phe	Gly	Val	Phe 75	Cys	Lys	Phe	Met	Gly 80
	Val	Val	Met	Ile	Phe 85	Phe	Gly	Leu	Ser	Pro 90	Leu	Leu	Leu	Gly	Ala 95	Ala
15	Met	Ala	Ser	Glu 100	Arg	Tyr	Leu	Gly	Ile 105	Thr	Arg	Pro	Phe	Ser 110	Arg	Pro
	Ala	Val	Ala 115	Ser	Gln	Arg	Arg	Ala 120	Trp	Ala	Thr	Val	Gly 125	Leu	Val	Trp
	Ala	Ala 130	Ala	Leu	Ala	Leu	Gly 135	Leu	Leu	Pro	Leu	Leu 140	Gly	Val	Gly	Arg
20	Tyr 145	Thr	Val	Gln	Tyr	Pro 150	Gly	Ser	Trp	Cys	Phe 155	Leu	Thr	Leu	Gly	Ala 160
	Glu	Ser	Gly	Asp	Val 165	Ala	Phe	Gly	Leu	Leu 170	Phe	Ser	Gly	Lev	Ser 175	Val
25	Gly	Leu	Ser	Phe 180	Leu	Leu	Asn	Thr	Val 185	Ser	Val	Ala	Thr	Leu 190	His	His
	Val	Tyr	His 195	Gly	Gln	Glu	Ala	Ala 200	Gln	Gln	Arg	Pro	Arg 205	Asp	Ser	Glu
	Val	Glu 210	Met	Met	Ala	Gln	Leu 215	Leu	Gly	Ile	Met	Val 220	Val	Ala	Ser	Val
30	Сув 225		Leu	Pro	Leu	Leu 230	Val	Phe	Ile	Ala	Gln 235	Thr	Val	Leu	Arg	Asn 240
	Pro	Pro	Ala	Met	Ser 245		Ala	Gly	Gln	Leu 250		Arg	Thr	Thr	Glu 255	Lys
35	Glu	Leu	Leu	Ile 260		Leu	Arg	Val	Ala 265		Trp	Asn	Gln	Ile 270	Leu	Asp
	Pro	Trp	Val 275		Ile	Leu	Phe	Arg 280		Ala	Val	Leu	Arg 285		Leu	Gln
	Pro	Arg 290		Ser	Thr	Arg	Pro 295		Ser	Leu	Ser	Leu 300		Pro	Gln	Leu
40	Th: 305		Arg	Ser	Gly	Leu 310										

LENGTH AMILE

TYPE amile acto

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

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	(ii)	MOLI	CULE	TYP	E: F	epti	de									
		SEQU Tyr						~			Val	Phe	Leu	Leu	Ser 15	Leu
5	Leu	Gly	Asn	Ser 20	Leu	Val	Met	Leu	Val 25	Ile	Leu	Tyr	Ser	Arg 30	Gly	Val
	Arg	Ser	Val 35	Thr	Ile	Val	Tyr	Leu 40	Leu	Asn	Ile	Ala	Ile 45	Ala	Asp	Leu
10	Leu	Phe 50	Ala	Leu	Thr	Leu	Pro 55	Ile	Trp	Ala	Ala	Ser 60	Lys	Val	Asn	Gly
	Trp 65	Ile	Phe	Gly	Thr	Phe 70	Leu	Cys	Lys	Trp	Ser 75	Leu	Leu	Lys	Glu	Val 80
	Asn	Phe	Tyr	Ser	Gly 85	Ile	Leu	Leu	Leu	Ala 90	Cys	Ile	Ser	Val	Asp 95	Arg
15	Tyr	Leu	Ala	Ile 100	Val	Arg	Ala	Thr	Arg 105	Thr	Leu	Thr	Gln	Lys 110	Arg	His
	Leu	Val	Lys 115	Phe	Ile	Cys	Leu	Ser 120	Ile	Trp	Gly	Leu	Ser 125	Leu	Leu	Leu
20	Ala	Leu 130	Pro	Val	Leu	Leu	Phe 135	Arg	Arg	Thr	Val	Tyr 140	Ser	Ser	Asn	Val
	Ser 145	Pro	Ala	Cys	Tyr	Glu 150	Asp	Met	Gly	Asn	Asn 155	Tyr	Ala	Asn	Trp	Arg 160
	Met	Leu	Leu	Pro	Ile 165	Leu	Pro	Gln	Ser	Phe 170	Gly	Phe	Ile	Val	Pro 175	Leu
25	Leu	Ile	Met	Leu 180	Tyr	Суѕ	Tyr	Gly	Phe 185	Thr	Leu	Arg	Thr	Leu 190	Phe	Lys
	Ala	Ile	Met 195	Gly	Gln	Lys	His	Arg 200	Ala	Met	Arg	Val	Ile 205	Phe	Ala	Val
30	Val	Leu 210	Ile	Phe	Leu	Leu	Cys 215	Trp	Leu	Pro	Tyr	Asn 220	Leu	Val	Leu	Il∈
	Ala 225	Asp	Thr				Thr						Thr	Cys		Arc 240
	Arg	Asn	His	Ile	Asp 245	Arg	Ala	Ile	Asp	Ala 250	Thr	Glu	Ile	Leu	Gly 255	Ile
35	Leu	His	Ser	Cys 260	Leu	Asn	Pro	Leu	Ile 265	Tyr	Ala	Phe	Ile	Gly 270	Gln	Lys
	Phe	Arg	His 275	Gly	Leu	Leu	Lys	Ile 280	Leu	Ala	Ile	His	Gly 285	Leu	Ile	Ser
40	Lys	Asp 290	Ser	Leu	Pro	Lys	As p 295	Ser	Arg	Pro	Ser	Phe 300	Val	Gly	Ser	Ser
	Ser 305	Gly	His	Thr	Ser	Thr 310	Thr	Leu								
45		RMAT SEQ (A (B	UENC:	E CH	ARĀC' : 32	TERI. 6 am	STIC	S:	s							

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	(ii)		TOP		Y: 1	inea	x.	e								
	(xi)	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	39:						
5	Leu 1	Phe	Pro	Ile	Val 5	Tyr	Ser	Ile	Ile	Phe 10	Val	Leu	Gly	Ile	Ile 15	Ala
	naA	Gly	Tyr	Val 20	Leu	Trp	Val	Phe	Ala 25	Arg	Leu	Tyr	Pro	Ser 30	Lys	Lys
10	Asn	Glu	Ile 35	Lys	Ile	Phe	Met	Val 40	Asn	Leu	Thr	Val	Ala 45	Asp	Leu	Leu
	Phe	Leu 50	Ile	Thr	Leu	Pro	Leu 55	Trp	Ile	Val	Tyr	Tyr 60	Ser	Asn	Gln	Gly
	Asn 65	Trp	Phe	Leu	Pro	Lys 70	Phe	Leu	Сув	Asn	Leu 75	Ala	Gly	Cys	Leu	Phe 80
15	Phe	Ile	Asn	Thr	Tyr 85	Сув	Ser	Val	Ala	Phe 90	Leu	Gly	Val	Ile	Thr 95	Tyr
	Asn	Arg	Phe	Gln 100	Ala	Val	Lys	Tyr	Pro 105	Ile	Lys	Thr	Ala	Gln 110	Ala	Thr
20	Thr	Arg	Lys 115	Arg	Gly	Ile	Ala	Leu 120	Ser	Leu	Val	Ile	Trp 125	Val	Ala	Ile
	Val	Ala 130	Ala	Ala	Ser	Tyr	Phe 135	Leu	Val	Met	Met	Asp 140	Ser	Thr	Asn	Val
	Val 145	Ser	Asn	Lys	Ala	Gly 150	Ser	Gly	Asn	Ile	Thr 155	Arg	Cys	Phe	Glu	Arg 160
25	Tyr	Glu	Lys	Gly	Ser 165	Lys	Pro	Val	Leu	Ile 170	Ile	His	Ile	Cys	Ile 175	Val
	Leu	Gly	Phe	Phe 180	Ile	Val	Phe	Leu	Leu 185	Ile	Leu	Phe	Cys	Asn 190	Leu	Val
30	Ile	Ile	His 195	Thr	Leu	Leu	Arg	Gly 200	Pro	Val	Lys	Gln	Gln 205	Arg	Asn	Ala
	Glu	Val 210		Arg	Arg	Ala	Leu 215	Trp	Met	Val	Cys	Thr 220	Val	Ile	Ala	Val
	Phe	Val	Ile	Cys	Phe	Val	Pro	His	His	Met	Val	Gln	Leu	Pro	Trp	Thr

40 275 280 285

245

Leu Ala Glu Leu Cly Met Trp Pro Ser Ser Asn His Gln Ala Ile Asn

Asp Ala His Gln Val Thr Leu Cys Leu Leu Ser Thr Asn Cys Val Leu 260 265 270

Asp Pro Val Ile Tyr Cys Phe Leu Thr Lys Lys Phe Arg Lys His Leu

45 Val Asn Pro Ile Lys Asn

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5	(2)	INFOF	SEQU (A) (B) (C) (D)	ENCE LEN TYI STI TOI	CHANGTH: PE: 6 CANDE POLOC	ARACT : 333 emino EDNES SY: 1	TERIS ami aci SS: s linea	STICS ino a id singl	S: acids	5							
10		(xi) Tyr 1	SEQU Ile									Phe	Val	Leu	Gly	Ile 15	Ile
		Gly	Asn	Ser	Thr 20	Leu	Leu	Arg	Ile	Ile 25	Tyr	Lys	Asn	Lys	Суз 30	Met	Arg
15		Asn	Gly	Pro 35	Asn	Ile	Leu	Ile	Ala 40	Ser	Ile	Ala	Leu	Gly 45	qaA	Leu	Leu
		His	Ile 50	Ile	Ile	Asp	Ile	Pro 55	Ile	Met	Ala	Tyr	Lys 60	Leu	Ile	Ala	Gly
		Asp 65	Trp	Pro	Phe	Ala	Cys 70	Lys	Leu	Phe	Pro	Phe 75	Leu	Gln	Lys	Ser	Ser 80
20		Val	Gly	Ile	Thr	Val 85	Leu	Asn	Leu	Cys	Ala 90	Leu	Ser	Val	qaA	Arg 95	Tyr
		Arg	Ala	Val	Ala 100	Ser	Trp	Ser	Arg	Val 105	Gln	Gly	Ile	Gly	Ile 110	Pro	Leu
25			Thr	115					120					125			
		Ala	Ile 130	Pro	Glu	Ala	Ile	Gly 135	Phe	Trp	Met	Val	Pro 140	Phe	Glu	Tyr	Lys
		Gly 145	Ala	Gln	His	Arg	Thr 150	Cys	Met	Leu	Asn	Ala 155	Thr	Ser	Lys	Leu	Phe 160
30		Tyr	Gln	Asp	Val	Lys 165	Asp	Trp	Trp	Leu	Phe 170	Gly	Phe	Tyr	Phe	Leu 175	Leu
			Сув		180					185					190		
35		Arg	Arg	Asn 195	Gly	Ser	Leu	Arg	Ile 200	Ala	Leu	Ser	Glu	His 205	Leu	Lys	Gln
			Arg 210				_	215			_		220				
		Leu 225	Сув	Trp	Phe	Pro	Leu 230	His	Leu	Ser	Arg	Ile 235	Leu	Lys	Lys	Thr	Val 240
40		Tyr	Asp	Glu	Met	Asp 245	Thr	Asn	Arg	Cys	Glu 250	Leu	Leu	Ser	Phe	Leu 255	Leu
		Leu	Met	Tyr	Ile 260	Gly	Ile	Asn	Thr	Ala 265	Thr	Met	Ser	Cys	Ile 270	Asn	Pro
45			Ala	275	-				280			_		285			
		Cys	Leu 290	Cys	Cys	Cys	Cys	Tyr 295	Gln	Ser	Lys	Ser	Ile 300	Met	Thr	Ser	Val

3.50 (10 million 20 million 44 million 45)

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Pro Met Gln Gly Thr Ser Ile Gln Trp Lys Asn His Glu Gln Asn Asn

		His	Asn	Thr	Glu	Arg 325	Ser	Ser	His	Lys	Asp 330	Ser	Ile	Asn			
5	(2)	INFOR	SEQU (A) (B) (C) (D)	ENCE LEN TYP STR TOP	CHA GTH: E: a ANDE OLOG	RACT 350 mino DNES Y: 1	ERIS ami aci S: s inea	TICS no a .d singl	cids	:							
		(xi) Leu l	SEQU Ile	ENCE Ala	DES Ser	CRIP Pro 5	TION Trp	I: SE Phe	Q II Ala	NO: Ala	41: Ser 10	Phe	Сув	Val	Val	Gly 15	Leu
15		Ala	Ser	Asn	Leu 20	Leu	Ala	Leu	Ser	Val 25	Leu	Ala	Gly	Ala	Arg 30	Gln	Ser
		Ser	Ser	His 35	Thr	Arg	Ser	Ser	Phe 40	Leu	Thr	Phe	Leu	Сув 45	Gly	Leu	Val
20		Leu	Thr 50	Leu	Ąsp	Phe	Leu	Gly 55	Leu	Leu	Val	Thr	Gly 60	Thr	Ile	Val	Val
		Ser 65	Gln	His	Ala	Ala	Leu 70	Phe	Glu	Trp	His	Ala 75	Val	Asp	Pro	Gly	Cys 80
		Arg	Leu	Сув	Arg	Leu 85	Val	Pro	Phe	Ile	Gln 90	Lys	Ala	Ser	Val	Gly 95	Ile
25		Thr	Val	Leu	Ser 100	Leu	Сув	Ala	Leu	Ser 105	Ile	Asp	Arg	Tyr	Arg 110	Ala	Val
		Ala	Ser	Trp 115	Ser	Arg	Ile	Lys	Gly 120	Ile	Gly	Val	Pro	Lys 125	Trp	Thr	Ala
30		Val	Glu 130	Ile	Val	Leu	Ile	Trp 135	Val	Val	Ser	Val	Val 140	Leu	Ala	Val	Pro
		Glu 145	Ala	Ile	Gly	Phe	As p 150		Thr	Ser	qaA	Tyr 155	Lys	Gly	Lys	Pro	Leu 160
		Arg	Val	Сув	Met	Leu 165		Pro	Phe	Gln	Lys 170		Ala	Phe	Met	Phe 175	Tyr
35		Lys	Thr	Ala	Ala 180		Asp	Trp	Trp	Leu 185		Ala	Phe	Tyr	Phe 190	Cys	Leu
		Pro	Leu	Ala 195		Thr	Ala	Ile	Phe 200		Thr	Leu	Met	Thr 205	Cys	Glu	Met
40		Leu	Arg 210		Lys	Ser	Gly	Met 215		Ile	Ala	. Leu	220	Asp	His	Leu	Lys
		Gln 225		Arg	Glu	Val	Ala 230		Thr	. Val	Phe	235	Let	Val	Leu	. Val	Phe 240
				-		ū		•	7.7 -				. +15	* ~ .	* ***		The se

Leu Val Leu Asp Tyr Ile Gly Ile Asn Met Ala Ser Ile Asn Ser Cys

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			275					280					285			
	Ile	Asn 290	Pro	Ile	Ala	Leu	Tyr 295	Leu	Val	Ser	Lys	Arg 300	Phe	Lys	Asn	Cys
5	Phe 305	Lys	Ser	Cys	Leu	Cys 310	Cys	Trp	Cys	Gln	Thr 315	Phe	Glu	Glu	Lys	Gln 320
	Ser	Leu	Glu	Glu	Lys 325	Gln	Ser	Cys	Leu	Lys 330	Phe	Lys	Ala	Asn	As p 335	His
	Gly	Tyr	Asp	Asn 340	Phe	Arg	Ser	Ser	Asn 345	Lys	Tyr	Ser	Ser	Ser 350		
10	(2) INFO	SEQU (A) (B) (C)	ION F JENCE LEN TYF STF	CHA IGTH: PE: & LANDE	ARACT 328 mino DNES	reris 3 ami 5 aci 5S: s	STICS ino a id singl	S: acids	5							
13	(ii)															
	Ile		JENCE Val		Pro					Leu	Ile	Ile	Val	Ile		Leu
20	l Ile	Gly	Asn	Ile 20	5 Thr	Leu	Ile	Lys	Ile 25	10 Phe	Cys	Thr	Val	Lys 30	15 Ser	Leu
	Asn	Leu	Phe 35	Ile	Ser	Ser	Ile	Ala 40	Leu	Gly	Asp	Leu	Leu 45	Leu	Leu	Val
25	Thr	Ile 50	Cys	Ala	Pro	Val	As p 55	Ala	Ser	Lys	Tyr	Ile 60	Ala	Asp	Arg	Trp
	Leu 65	Phe	Gly	Arg	Ile	Gly 70	Cys	Lys	Leu	Ile	Pro 75	Phe	Ile	Gln	Leu	Thr 80
	Ser	Val	Gly	Val	Ser 85	Val	Phe	Thr	Leu	Thr 90	Ala	Leu	Ser	Ala	Asp 95	Arg
30	Tyr	Lys	Ala	11e 100	Val	Arg	Pro	Thr	Cys 105	Ile	Gln	Ala	Ser	Leu 110	Ile	Cys
	Leu	Lys	Ala 115	Ala	Leu	Ile	Trp	Ile 120	Val	Ser	Leu	Leu	Ala 125	Ile	Pro	Glu
35	Ala	Val 130	Phe	Ser	Asp	Leu	His 135	Pro	Phe	His	Val	Lys 140	Asp	Thr	Asn	Gln
	Thr 145	Phe	Ile	Ser	Cys	Ala 150	Pro	Tyr	Pro	His	Ser 155	Asn	Glu	Leu	His	Pro 160
	Lys	Ile	His	Ser	Met 165	Ala	Ser	Phe	Leu	Val 170	Phe	Tyr	Val	Ile	Pro 175	Leu
40	Ala	Ile	Ile	Ser 180	Val	Tyr	Tyr	Tyr	Phe 185	Ile	Ala	Arg	Asn	Leu 190	Ile	Gln
	Ser	Ala	Tyr 195	Asn	Leu	Pro	Val	Glu 200	Gly	Asn	Ile	His	Val 205	Lys	Lys	Gln
45	Ile	Glu 210	Ser	Arg	Lys	Arg	Leu 215	Ala	Lys	Thr	Val	Leu 220	Val	Phe	Val	Gly
	Leu 225	Phe	Ala	Phe	Cys	Trp 230	Leu	Pro	Asn	His	Val 235	Ile	Tyr	Leu	Tyr	Arg 240

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		Ser	Tyr	His	Tyr	Ser 245	Glu	Val	Asp	Thr	Ser 250	Met	Leu	His	Phe	Val 255	Thr
		Ser	Ile	Cys	Ala 260	Arg	Leu	Leu	Ala	Pro 265	Thr	Asn	Ser	Cys	Val 270	Asn	Pro
5		Phe	Ala	Leu 275	Tyr	Leu	Leu	Ser	Lys 280	Ser	Phe	Arg	Gln	Phe 285	Asn	Thr	Gln
		Leu	Leu 290	Cys	Сув	Gln	Pro	Gly 295	Leu	Ser	His	Ser	Thr 300	Gly	Arg	Ser	Leu
10		Ser 305	Phe	Lys	Ser	Thr	Asn 310	Pro	Ser	Ala	Thr	Phe 315	Ser	Leu	Ile	Asn	Arg 320
		naA	Ile	Суѕ	His	Glu 325	Gly	Tyr	Val								
15	(2)	INFOR	SEQU (A) (B) (C) (D)	JENCE LEN TYI STI TOI	CHA IGTH: PE: & CANDE POLOC	RACT 345 mino SDNES SY: J	TERIS ami aci SS: s Linea	STICS ino a id sing]	S: acids	5							
20		(xi)	SEQ	JENCE	DES	CRIE	- TIOI	1: SI									
		Cys 1	Val	Ile	Pro	Ser 5	Ser	Leu	Tyr	Leu	Ile 10	Ile	Ile	Ser	Val	Gly 15	Leu
		Leu	Gly	Asn	Ile 20	Met	Leu	Val	Lys	Ile 25	Phe	Leu	Thr	Asn	Ser 30	Thr	Met
25		Arg	Ser	Val 35	Pro	Asn	Ile	Phe	Ile 40	Ser	Asn	Ile	Ala	Ala 45	Glir	Asp	Leu
		Leu	Leu 50	Leu	Leu	Thr	Cys	Val 55	Pro	Val	Asp	Ala	Ser 60	Arg	Tyr	Phe	Phe
30		Asp 65	Glu	Trp	Val	Phe	Gly 70	Lys	Leu	Ile	Gly	Cys 75	Lys	Leu	Ile	Pro	Ala 80
		Ile	Gln	Leu	Thr	Ser 85	Val	Gly	Val	Ser	Val 90	Pro	Thr	Leu	Thr	Ala 95	Leu
		Ser	Ala	Asp	Arg 100	Tyr	Arg	Ala	Ile	Val 105	Asn	Pro	Met	Asp	Met 110	Thr	Ser
35		Gly	Val	Val 115	Leu	Trp	Thr	Ser	Val 120	Ala	Val	Gly	Ile	Trp 125	Val	Val	Ser
		Val	Leu 130	Leu	Ala	Val	Pro	Glu 135	Ala	Val	Phe	Ser	Glu 140	Val	Ala	Arg	Ile
40		Gly 145	Ser	Ser	qaA	Asn	Ser 150	Ser	Phe	Thr	Ala	Сув 155	Ile	Pro	Tyr	Pro	Gln 160
		Thr	Asp	Glu	Leu	His 165	Pro	Lys	Ile	His	Ser 170	Val	Leu	Ile	Phe	Leu 175	Val
															-		

Glu His Thr Lys Lys Gln Met Glu Thr Arg Lys Arg Leu Ala Lys Ile

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			210					215					220				
		al 25	Leu	Val	Phe	Val	Gly 230	Cys	Phe	Val	Phe	Cys 235	Trp	Phe	Pro	Asn	His 2 4 0
5	I	le	Leu	Tyr	Leu	Tyr 245	Arg	Ser	Phe	Asn	Tyr 250	Lys	Glu	Ile	Asp	Pro 255	Ser
	L	eu	Gly	Thr	Cys 260	Val	Thr	Leu	Val	Ala 265	Arg	Val	Leu	Ser	Phe 270	Ser	Asn
	S	er	Cys	Val 275	Asn	Pro	Phe	Ala	Leu 280	Tyr	Leu	Leu	Ser	Glu 285	Ser	Phe	Arg
10	L	ys	His 290	Phe	Ser	Asn	Gln	Leu 295	Cys	Cys	Gly	Gln	Lys 300	Ser	Tyr	Pro	Glu
		rg 105	Ser	Thr	Ser	Tyr	Leu 310	Leu	Ser	Ser	Ser	Ala 315	Val	Trp	Arg	Ser	Leu 320
15	L	ys	Ser	Asn	Ala	Lув 325	Asn	Val	Val	Thr	Asn 330	Ser	Val	Leu	Ile	Asn 335	Gly
	H	lis	Ser	Thr	Lys 340	Gln	Glu	Ile	Ala	Leu 345							
20	((i)	SEQU (A) (B) (C) (D)	JENCI LEI TYI STI	E CHA NGTH PE: 8 RANDI POLO	SEQ : ARACT : 316 amino EDNES SY: :	reris am: ac: ss: s linea	ino a id singl	S: acids	5							
25	x) T L	yr	SEQT Thr	JENCI Leu	E DES Ser	SCRII Phe 5	PTION Ile	1: SI Tyr	EQ II Ile	NO Phe	:44: Ile 10	Phe	Val	Ile	Cys	Glx 15	Leu
25	ב ב	(yr	Thr	Leu	Ser	Phe 5	Ile	Tyr	Ile	Phe	Ile 10						
30	1 1	Tyr Leu	Thr	Leu Asn	Ser Ser 20	Phe 5 Val	Ile Val	Tyr Val	Ile	Phe Val 25	Ile 10 Asn	Ile	Gln	Ala	Lys 30	15	Thr
	1 1	Cyr Leu Eeu	Thr Ala Tyr	Asn Asp 35	Ser Ser 20 Thr	Phe 5 Val His	Ile Val Cys	Tyr Val Tyr	Trp	Val 25 Leu	Ile 10 Asn Asn	Ile Leu	Gln Ala	Ala Ile 45	Lys 30 Ala	15 Thr	Thr
	1 1 0	Tyr Leu Ely Trp	Thr Ala Tyr Trp 50	Asn Asp 35 Leu	Ser Ser 20 Thr	Phe 5 Val His	<pre>Ile Val Cys Pro</pre>	Tyr Val Tyr Val 55	Trp Ile 40 Trp	Phe Val 25 Leu Trp	Ile 10 Asn Asn Ser	Ile Leu Leu	Gln Ala Val 60	Ala Ile 45 Gln	Lys 30 Ala His	Thr Asp Asn	Thr
30		Leu Ely Trp	Thr Ala Tyr Trp 50 Pro	Asn Asp 35 Leu Met	Ser 20 Thr Thr	Phe 5 Val His Ile Glu	Val Cys Pro Leu 70	Tyr Val Tyr Val 55 Thr	Trp Ile 40 Trp Cys	Val 25 Leu Trp	Ile 10 Asn Asn Ser Val	Ile Leu Leu Thr	Gln Ala Val 60 His	Ala Ile 45 Gln Leu	Lys 30 Ala His	Thr Asp Asn	Thr Leu Gln Ser
30		Tyr Leu Sly Trp Frp	Thr Ala Tyr Trp 50 Pro Asn	Asn Asp 35 Leu Met	Ser 20 Thr Thr Gly Phe	Phe 5 Val His Ile Glu Ser 85	Val Cys Pro Leu 70 Gly	Tyr Val Tyr Val 55 Thr	Trp Ile 40 Trp Cys	Val 25 Leu Trp Lys	Ile 10 Asn Asn Ser Val Leu 90	Ile Leu Thr 75	Gln Ala Val 60 His	Ala Ile 45 Gln Leu Met	Lys 30 Ala His Ile Ser	Thr Asp Asn Phe Val	Thr Leu Gln Ser 80 Asp
30		Tyr Leu Gly Trp Trp 55 Ile	Thr Ala Tyr Trp 50 Pro Asn Tyr	Asn Asp 35 Leu Met Leu Leu	Ser Ser 20 Thr Thr Gly Phe Ser 100	Phe 5 Val His Ile Glu Ser 85 Ile	Val Cys Pro Leu 70 Gly Thr	Tyr Val Tyr Val 55 Thr Ile	Trp Ile 40 Trp Cys Phe	Phe Val 25 Leu Trp Lys Phe Thr 105	Ile 10 Asn Asn Ser Val Leu 90 Asn	Ile Leu Thr 75 Thr	Gln Ala Val 60 His Cys	Ala Ile 45 Gln Leu Met	Lys 30 Ala His Ile Ser Se:	Thr Asp Asn Phe Val 95 Arg	Thr Leu Gln Ser 80 Asp
30		Tyr Leu Gly Trp Trp 555 Ile Arg	Thr Ala Tyr Trp 50 Pro Asn Tyr Met	Asn Asp 35 Leu Met Leu Val 115	Ser 20 Thr Thr Gly Phe Ser 100 Arg	Phe 5 Val His Ile Glu Ser 85 Ile Arg	Val Cys Pro Leu 70 Gly Thr	Tyr Val Tyr Val 55 Thr Ile Tyr Val	Trp Ile 40 Trp Cys Phe Phe Cys 120	Val 25 Leu Trp Lys Phe Thr 105 Ile	Ile 10 Asn Asn Ser Val Leu 90 Asn Leu	Ile Leu Thr 75 Thr Val	Gln Ala Val 60 His Cys Pro	Ala Ile 45 Gln Leu Met Ser Leu 125	Lys 30 Ala His Ile Ser 110 Leu	Thr Asp Asn Phe Val 95 Arg	Thr Leu Gln Ser 80 Asp
30		Tyr Leu Gly Trp Trp 65 Ile Arg Lys	Thr Ala Tyr Trp 50 Pro Asn Tyr Met Val	Asp 35 Leu Met Leu Val 115 Ser	Ser 20 Thr Thr Gly Phe Ser 100 Arg Leu	Phe 5 Val His Ile Glu Ser 85 Ile Arg	Val Cys Pro Leu 70 Gly Thr Ala Asp	Tyr Val Tyr Val Thr Ile Tyr Val Thr 135	Trp Ile 40 Trp Cys Phe Phe Cys 120 Tyr	Val 25 Leu Trp Lys Phe Thr 105 Ile	Ile 10 Asn Asn Ser Val Leu 90 Asn Leu Leu	Ile Leu Leu Thr 75 Thr Val Lys	Gln Ala Val 60 His Cys Pro Trp Thr 140	Ala Ile 45 Gln Leu Met Ser Leu 125 Val	Lys 30 Ala His Ile Ser Se: 110 Leu	Thr Asp Asn Phe Val 95 Arg Ala Ser	Thr Leu Gln Ser 80 Asp Lys

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		Ala	Val	Pro	Phe 180	Ser	Ile	Ile	Ala	Val 185	Phe	Tyr	Phe	Ser	Leu 190	Ile	Ala
		Arg	Ala	Ile 195	Ser	Ala	Ser	Ser	Asp 200	Gln	Glu	Lys	His	Ser 205	Ser	Arg	Lys
5		Ile	Ile 210	Phe	Ser	Tyr	Val	Val 215	Val	Phe	Leu	Val	Cys 220	Trp	Leu	Pro	Tyr
		His 225	Val	Ala	Val	Leu	Leu 230	Asp	Ile	Phe	Ser	Ile 235	Leu	His	Tyr	Ile	Pro 240
10		Phe	Thr	Cys	Arg	Leu 245	Glu	His	Ala	Leu	Phe 250	Thr	Ala	Leu	His	Val 255	Thr
		Gln	Cys	Leu	Ser 260	Leu	Val	His	Сув	Cys 265	Val	Asn	Pro	Val	Leu 270	Tyr	Ser
		Phe	Ile	Asn 275	Arg	Asn	Tyr	Arg	Tyr 280	Glu	Ile	Asn	Trp	Ile 285	Phe	Lys	Tyr
15		Ser	Ala 290	Lys	Thr	Gly	Leu	Thr 295	Lys	Leu	Ile	Asp	Ala 300	Ser	Arg	Val	Ser
		Glx 305	Thr	Glu	Tyr	Ser	Ala 310	Leu	Glu	Gln	Asn	Ala 315	Lys				
20	(2) I		SEQT (A)	JENCE LEN	CHANGTH:		reris	TICS		3							
25	((ii)	(C)	STI TOI	RANDE POLOC	EDNES SY: :	SS: a linea	sing: ar	le								
25			(C) (D) MOLE	STI TOI CULI	RANDI POLOC E TYI	SDNES SY: : PE: :	SS: a linea pept:	sing: ar ide		NO.	· 45 ·						
25	((xi)	(C) (D) MOLE SEQU	STI TOI ECULI JENCI	RANDI POLOC E TYI E DES	EDNES GY: : PE: : : SCRII	SS: a linea pept: PTIO	sing] ar ide N: SI	le EQ II Tyr			Leu	Phe	Val	Va≟	Gly 15	Thr
25 30	((xi) Lys l	(C) (D) MOLE SEQU Val	STI TOI ECULI JENCI Leu	RANDI POLOC E TYI E DES Val	EDNES FY: I PE: p SCRII Thr 5	SS: a linea pept: PTION Ala	sing ar ide N: SI Ile	EQ II	Leu	Ala 10					15	
	((xi) Lys l Val	(C) (D) MOLE SEQU Val	STI TOI SCULI JENCI Leu Asn	RANDE POLOCE TYPE E DES Val Ser 20	EDNES GY: I PE: I SCRII Thr 5 Val	SS: silines pept: PTION Ala Thr	sing ar ide N: SI Ile	EQ II Tyr	Leu Thr 25	Ala 10 Leu	Ala	Arg	Lys	Lys 30	15 Ser	Leu
	((xi) Lys l Val	(C) (D) MOLE SEQU Val Gly Ser	STIP TOI SCULI JENCI Leu Asn Leu 35	RANDE POLOCE TYPE E DES Val Ser 20	SDNES GY: I PE: I SCRII Thr 5 Val	SS: alineapept: PTION Ala Thr	sing ar ide N: SI Ile Ala Val	EQ II Tyr Phe His	Thr 25 Tyr	Ala 10 Leu His	Ala Leu	Arg Ser	Lys Ser 45	Lys 30 Leu	Ser	Leu Leu
	((xi) Lys l Val Gln	(C) (D) MOLE SEQU Val Gly Ser Asp 50	STI TOI SCULI JENCI Leu Asn Leu 35	Ser 20 Gln	SDNES SY: F SCRII Thr 5 Val Ser	SS: alineapept: PTION Ala Thr Thr	sing: ar ide N: SI Ile Ala Val Leu 55	EQ II Tyr Phe His	Thr 25 Tyr Val	Ala 10 Leu His	Ala Leu Leu	Arg Ser Tyr 60	Lys Ser 45 Asn	Lys 30 Leu Phe	Ser Ala Ile	Leu Leu Trp
30	((xi) Lys 1 Val Gln Ser His	(C) (D) MOLE SEQU Val Gly Ser Asp 50 His	STIP TOP TOP TOP TOP TOP TOP TOP TOP TOP TO	Ser 20 Gln Leu	SDNES SY: F SCRIN Thr 5 Val Ser Ile Ala	SS: alineacoept: PTION Ala Thr Thr Leu Phe 70	sing: ar ide N: SI Ile Ala Val Leu 55 Gly	EQ II Tyr Phe His 40	Thr 25 Tyr Val	Ala 10 Leu His Glu Gly	Ala Leu Leu Cys 75	Arg Ser Tyr 60 Arg	Lys Ser 45 Asn	Lys 30 Leu Phe	Ser Ala Ile Tyr	Leu Trp Phe
30	((xi) Lys 1 Val Gln Ser His 65 Leu	(C) (D) MOLE SEQU Val Gly Ser Asp 50 His	STIP TOP TOP TOP TOP TOP TOP TOP TOP TOP TO	Ser 20 Gln Leu Trp	SONES SY: SPE: PE: PE: PE: PE: PE: PE: PE: PE: PE:	SS: alineacoept: PTION Ala Thr Thr Leu Phe 70 Thr	sing: ar ide N: SI Ile Ala Val Leu 55 Gly Tyr	EQ II Tyr Phe His 40 Trp Asp	Thr 25 Tyr Val Ala Thr	Ala 10 Leu His Glu Gly Ala 90	Ala Leu Leu Cys 75 Leu	Arg Ser Tyr 60 Arg	Lys Ser 45 Asn Gly Val	Lys 30 Leu Phe Tyr	Ser Ala Ile Tyr Ser 95	Leu Trp Phe 80 Leu

Ile Val Asp Thr Ala Thr Val Lys Val Val Ile Gln Val Asn Thr Phe

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						165					170					175	
		Met	Ser	Phe	Leu 180	Phe	Pro	Met	Leu	Val 185	Ile	Ser	Ile	Leu	Asn 190	Thr	Val
5		Ile	Ala	Asn 195	Lys	Leu	Thr	Val	Met 200	Val	His	Gln	Ala	Ala 205	Glu	Gln	Gly
		Arg	Val 210	Cys	Thr	Val	Gly	Thr 215	His	Asn	Gly	Leu	Glu 220	His	Ser	Thr	Phe
		Asn 225	Met	Arg	Ile	Glu	Pro 230	Gly	Arg	Val	Gln	Ala 235	Leu	Arg	His	Gly	Val 2 4 0
10		Leu	Val	Leu	Arg	Ala 245	Val	Val	Ile	Ala	Phe 250	Val	Val	Cys	Trp	Leu 255	Pro
		Tyr	Leu	Cys	Tyr 260	Ile	Ser	Asp	Glu	Gln 265	Trp	Arg	Thr	Phe	Leu 270	Phe	Asp
15		Phe	Tyr	His 275	Tyr	Phe	Tyr	Met	Leu 280	Thr	Asn	Ala	Leu	Phe 285	Tyr	Val	Ser
		Ser	Ala 290	Ile	Asn	Pro	Ile	Leu 295	Tyr	Asn	Leu	Val	Ser 300	Ala	Asn	Phe	Arg
		Gln 305	Val	Phe	Leu	Ser	Thr 310	Leu	Ala	Cys	Leu	Phe 315	Cys	Pro	Gly	Trp	Pro 320
20		Leu	Ile	Arg	Arg	Lys 325	Lys	Arg	Pro	Thr	Phe 330	Ser	Arg	Lys	Pro	Asn 335	Ser
		Met	Ser	Ser	Asn 340	His	Ala	Phe	Ser	Thr 345	Ser	Ala	Thr	Arg	Phe 350	Thr	Leu
25		Tyr															
30	(2)		SEQ	UENCI) LEI) TY!	E CH	ARAC : 31 amin	reri: 6 am: 5 ac:	STIC: ino a id	S: acid:	s							
		(ii)) TO: ECUL:													
35		(xi) Ala 1		UENC: Gln									Leu	Leu	Ala	Ala 15	Leu
		Glu	Asn	Ile	Phe 20	Val	Leu	Ser	Val	Phe 25	Cys	Leu	His	Lys	Thr 30	Asn	Cys
		Thr	Val	Ala 35	Glu	Ile	Tyr	Leu	Gly 40	Asn	Ile	Ala	Ser	Ala 45	Asp	Leu	Ile
40		Ile	Ala 50	Cys	Gly	Leu	Pro	Phe 55	Trp	Ala	Ile	Thr	Ile 60	Ala	Asn	Asn	Phe
		Asp 65	Trp	Leu	Phe	Gly	Glu 70	Val	Leu	Cys	Arg	Val 75	Val	Asn	Leu	Tyr	M et
45		Asn	Leu	Tyr	Ser	Ser 85	Ile	Cys	Phe	Leu	Val 90	Ser	Ile	Asp	Arq	Tyr 95	Leu
		Ala	Leu	Val	Lys 100	Thr	Met	Ser	Asn	Leu 105	Arg	Trp	Ala	Lys	Leu 110	Tyr	Ser

(Frank) Frank) (Albanier Art

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										10	-						
		Leu	Val	Ile 115	Trp	Ser	Cys	Thr	Leu 120	Leu	Leu	Ser	Ser	Pro 125	Met	Leu	Val
		Phe	Arg 130	Thr	Met	Tyr	Arg	Glu 135	Glu	Gly	His	Asn	Val 140	Thr	Суз	Val	Ile
5		Val 145	Tyr	Pro	Ser	Arg	Ser 150	Trp	Glu	Val	Phe	Leu 155	Leu	Asn	Leu	Val	Gly 160
		Phe	Leu	Leu	Pro	Leu 165	Ser	Ile	Ile	Thr	Phe 170	Cys	Thr	Val	Arg	Ile 175	Met
10		Val	Leu	Arg	Asn 180	Asn	Glu	Met	Lys	Lys 185	Phe	Lys	Glu	Val	Gln 190	Thr	Glu
		Lys	Lys	Ala 195	Thr	Val	Leu	Val	Ile 200	Ala	Val	Leu	Gly	Leu 205	Phe	Val	Leu
		Cys	Trp 210	Phe	Pro	Phe	Gln	Ile 215	Ser	Thr	Phe	Leu	Asp 220	Thr	Leu	Leu	Arg
15		Leu 225	Gly	Val	Leu	Ser	Gly 230	Cys	Trp	Asn	Glu	Arg 235	Ala	Val	Asp	Ile	Val 240
		Arg	Gln	Ile	Ser	Ser 245	Tyr	Val	Ala	Tyr	Ser 250	Asn	Ser	Cys	Leu	Asn 255	Pro
20		Leu	Val	Tyr	Val 260	Ile	Val	Gly	Lys	Arg 265	Phe	Arg	Lys	Lys	Ser 270	Arg	Glu
		Val	Tyr	Gln 275	Ala	Ile	Cys	Arg	Lys 280	Gly	Gly	Cys	Met	Gly 285	Glu	Ser	Val
		Leu	Asn 290	Ser	Met	Gly	Thr	Leu 295	Arg	Thr	Ser	Ile	Ser 300	Val	Asp	Arg	Gln
25		Ile 305	His	Lys	Leu	Gln	Asp 310	Trp	Ala	Gly	Asn	Lys 315	Gln				
30	(2)		SEQU (A) (B) (C)	JENCI LEI TYI STI	E CHI NGTH PE: 8 RANDI POLO	ARAC' : 34' emino EDNE:	reris 7 am: 5 ac: SS: s line	STICS ino a id sing: ar	S: acids	5							
35		(xi) Ile	SEQ Leu									Glv	Tle	Val	Gl:	Asn	Tle
		1				Ĺ					10					15	
			Val		20					25					30		
40		Val	Ser	Ile 35	Ala	Val	Ala	Asp	Leu 40	Met	Val	Leu	Val	Ala 45	Ala	Gly	Leu
		Pro	Asn 50	Ile	Thr	Asp	Ser	Ile 55	Tyr	Gly	Ser	Trp	Val 60	Tyr	Gly	Tyr	Val
		. "" *	2.5	. •			242.3	rin				. 51		:	23 2 14	'-	

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His Pro Ile Lys Ala Gln Phe Leu Cys Thr Phe Ser Arg Ala Lys Lys

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				100					105					110		
	Ile	Ile	Ile 115	Phe	Val	Trp	Ala	Phe 120	Thr	Ser	Ile	Tyr	Leu 125	Phe	Leu	Leu
5	Asp	Ile 130	Asn	Ile	Ser	Thr	Tyr 135	Lys	Asn	Ala	Val	Val 140	Val	Ser	Cys	Gly
	Tyr 145	Lys	Ile	Ser	Arg	Asn 150	Tyr	Tyr	Ser	Pro	Ile 155	Tyr	Leu	Met	Asp	Phe 160
	Gly	Val	Phe	Tyr	Val 165	Val	Pro	Leu	Ile	Ala 170	Thr	Val	Leu	Tyr	Gly 175	Phe
10	Ile	Ala	Arg	Ile 180	Leu	Phe	Leu	Asn	Pro 185	Ile	Pro	Ser	Asp	Pro 190	Lys	Glu
	Asn	Ser	Lys 195	Met	Trp	Lys	Asn	Asp 200	Ser	Ile	His	Gln	Asn 205	Lys	Asn	Leu
15	Asn	Leu 210	Asn	Ala	Ser	Ser	Arg 215	Lys	Gln	Val	Thr	Ile 220	Asn	Leu	Ala	Val
	Val 225	Val	Ile	Leu	Phe	Ala 230	Leu	Leu	Trp	Asn	Thr 235	Tyr	Arg	Thr	Leu	Val 240
	Val	Val	Asn	Ser	Phe 245	Leu	Ser	Ser	Pro	Phe 250	Gln	Glu	Asn	Trp	Lys 255	Leu
20	Leu	Lys	Cys	Arg 260	Ile	Cys	Ile	Tyr	Leu 265	Asn	Ser	Ala	Ile	Asn 270	Pro	Val
	Ile	Tyr	Asn 275	Ile	Met	Ser	Gln	Lys 280	Arg	Phe	Ala	Ala	Phe 285	Arg	Lys	Leu
25	Cys	Asn 290	Cys	Lys	Gln	Lys	Pro 295	Thr	Glu	Lys	Ala	Ala 300	Asn	Tyr	Ser	Val
	Ala 305	Leu	Asn	Tyr	Ser	Val 310	Ile	Lys	Glu	Ser	Asp 315	Arg	Phe	Ser	Thr	Glu 320
	Leu	Glu	Asp	Ile	Thr 325	Val	Thr	Asp	Thr	Tyr 330	Val	Ser	Thr	Thr	Lys 335	Val
30	Ser	Phe	qaA	Asp 340	Thr	Cys	Ile	Ala	Ser 345	Glu	Asn					
	(2) INFO	RMAT	I NOI	FOR S	SEQ :	ID N	0:48	:								
35	(i)	(A) (B) (C)) LEI) TYI) STI	NGTH PE: 8 RANDI	: 34: amino EDNE:	reris	ino a id sing:	acid	S							
	(ii)					line: pept										
40	(xi) Leu 1										Leu	Val	Leu	Va.	Ala 15	Val
	Thr	Gly	Asn	Ala 20	Ile	Val	Ile	Trp	Ile 25	Ile	Leu	Ala	His	Arg 30	Arg	Met
45	Arg	Thr	Val 35	Thr	Asn	Tyr	Phe	Ile 40	Val	Asn	Ile	Ala	Leu 45	Ala	Asp	Leu
	Leu	Asn	Ala	Ala	Phe	Asn	Phe	Val	Tyr	Ala	Ser	His	Asn	Ile	Trp	Tyr

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50 55 60 Phe Gly Arg Ala Phe Cys Tyr Phe Gln Asn Leu Phe Pro Ile Thr Ala Met Phe Val Ser Ile Tyr Ser Met Thr Ala Ile Ala Ala Asp Arg Tyr 5 Met Ala Ile Val His Pro Phe Gln Pro Arg Leu Ser Ala Pro Ser Thr 105 Lys Ala Val Ile Ala Gly Ile Trp Leu Val Ala Ile Lys Leu Ala Phe 10 Pro Gln Cys Phe Tyr Ser Thr Val Thr Met Gln Gly Ala Thr Lys Cys Val Val Ala Trp Pro Glu Asp Ser Gly Gly Lys Thr Leu Leu Leu Tyr His Leu Val Val Ile Ala Leu Ile Tyr Phe Leu Pro Ile Ala Leu Ala 15 Tyr Ser Val Ile Gly Leu Thr Leu Trp Arg Arg Ala Val Pro Gly His Gln Ala His Gly Ala Asn Leu Arg His Leu Gln Ala Lys Lys Lys Phe 20 Val Lys Thr Met Val Leu Val Val Val Thr Phe Ala Ile Cys Trp Leu 210 215 Pro Tyr His Leu Tyr Phe Ile Leu Gly Ser Phe Gln Glu Asp Ile Tyr Cys His Lys Phe Ile Gln Gln Val Tyr Leu Ala Leu Phe Trp Leu Ala 25 245 Met Ser Ser Thr Met Tyr Asn Pro Ile Ile Tyr Cys Cys Leu Asn His 265 Arg Phe Arg Ser Gly Phe Arg Leu Ala Phe Arg Cys Cys Pro Trp Val 280 30 Thr Pro Thr Lys Glu Asp Lys Leu Glu Leu Thr Pro Thr Thr Ser Leu 295 Ser Thr Arg Val Asn Arg Cys His Thr Lys Glu Thr Leu Phe Met Ala Gly Asp Thr Ala Pro Ser Glu Ala Thr Ser Gly Glu Ala Gly Arg Pro 35 330 Gln Asp Gly Ser Gly 340 (2) INFORMATION FOR SEQ ID NO:49:

(2) INFORMATION FOR SEQ ID NO:49: (i) SEQUENCE CHARACTERISTICS:

40

 $\frac{1}{2} \left(\frac{h_{k}}{h_{k}} \right) = -\frac{1}{2} \left(\frac{h_{k}}{h_{k}} \right) = -\frac{1}{2} \left(\frac{h_{k}}{h_{k}} \right) \left(\frac{h_{k}}{h_{k}} \right) \left(\frac{h_{k}}{h_{k}} \right) = -\frac{1}{2} \left(\frac{h_{k}}{h_{k}} \right) \left(\frac{h_{k}}{h_{k}} \right) \left(\frac{h_{k}}{h_{k}} \right) \left(\frac{h_{k}}{h_{k}} \right) = -\frac{1}{2} \left(\frac{h_{k}}{h_{k}} \right) \left$

(A) LENGTH: 340 amino acids

والمالونون المتكاف المستكاليفسا

xi; SEQUENCE DESCRIPTION: SEQ ID NC:49:
Ile Val Leu Trp Ala Ala Ala Tyr Thr Val Ile Val Val Arg Ser Val
1 5 10 15

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	Val	Gly	Asn	Val 20	Val	Val	Ile	Trp	Ile 25	Ile	Leu	Ala	His	Lys 30	Arg	Met
	Arg	Thr	Val 35	Thr	Asn	Tyr	Phe	Leu 40	Val	Asn	Ile	Ala	Phe 45	Ala	Phe	Ala
5	Leu	Asn 50	Thr	Trp	naA	Phe	Thr 55	Tyr	Ala	Val	His	Asn 60	Val	Trp	Tyr	Tyr
	Gly 65	Leu	Phe	Tyr	Cys	Lys 70	Phe	His	Asn	Phe	Phe 75	Pro	Ile	Ala	Ala	Leu 80
10	Phe	Ala	Ser	Ile	Tyr 85	Ser	Met	Thr	Ala	Val 90	Ala	Phe	Asp	Arg	Tyr 95	Leu
	Ile	Ile	His	Pro 100	Leu	Gln	Pro	Arg	Leu 105	Ser	Ala	Thr	Ala	Thr 110	Lys	Val
	Val	Ile	Phe 115	Val	Ile	Trp	Val	Ile 120	Ala	Leu	Leu	Leu	Ala 125	Ser	Pro	Gln
15	Gly	Tyr 130	Tyr	Ser	Thr	Thr	Glu 135	Leu	Ser	Arg	Val	Val 140	Cys	Met	Ile	Glu
	Trp 145	Pro	Glu	His	Pro	Asn 150	Arg	Thr	Tyr	Glu	Lys 155	Ala	Tyr	Hie	Ile	Cys 160
20	Val	Thr	Val	Leu	Ile 165	Tyr	Phe	Leu	Pro	Leu 170	Leu	Val	Ile	Gly	Tyr 175	Ala
	Tyr	Thr	Val	Val 180	Gly	Ile	Thr	Leu	Trp 185	Ala	Ser	Glu	Ile	Pro 190	Gly	Asp
	Ser	Ser	Asp 195	Arg	Tyr	His	Glu	Gln 200	Val	Ser	Ala	Lys	Arg 205	Lys	Val	Val
25	Lys	Met 210	Ile	Cys	Val	Val	Val 215	Cys	Thr	Phe	Ala	11e 220	Cys	Trp	Leu	Pro
	Phe 225	His	Val	Phe	Phe	Leu 230	Leu	Pro	Tyr	Ile	Asn 235	Pro	Asp	Leu	Tyr	Leu 240
30	Lys	Lys	Phe	Ile	Gln 2 4 5	Gln	Val	Tyr	Ile	Ala 250	Ser	Met	Trp	Leu	Ala 255	Met
	Ser	Ser	Thr	Met 260	Tyr	Asn	Pro	Ile	Ile 265	Tyr	Cys	Cys	Leu	Asn 270	Asp	Arg
	Phe	Arg	Leu 275	Gly	Phe	Lys	His	Ala 280	Phe	Arg	Cys	Cys	Pro 285	Phe	Ile	Ser
35	Ala	Gly 290	Asp	Tyr	Glu	Gly	Leu 295	Glu	Met	Ile	Lys	Ser 300	Thr	Arg	Tyr	Leu
	Gln 305	Thr	Leu	Ser	Ser	Val 310	Tyr	Lys	Val	Ser	Arg 315	Leu	Glu	Thr	Thr	Ile 320
40	Ser	Thr	Val	Val	Gly 325	Ala	His	Glu	Glu	Glu 330	Pro	Glu	Glu	Gly	Pro 335	Lys
	Ala	Thr	Pro	Ser 340												

- (2) INFORMATION FOR SEQ ID NO:50:

 (i) SEQUENCE CHARACTERISTICS:

 (A) LENGTH: 336 amino acids

 (B) TYPE: amino acid

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(C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

	(xi)	SEQ	JENCI	E DES	SCRI	PTIO	N: SI	EQ II	ON C	:50:						
5	Ile 1	Ala	Leu	Trp	Ser 5	Leu	Ala	Tyr	Gly	Leu 10	Val	Val	Ala	Val	Ala 15	Val
	Phe	Gly	Asn	Leu 20	Ile	Val	Ile	Trp	Ile 25	Ile	Leu	Ala	His	Lys 30	Arg	Met
10	Arg	Thr	Val 35	Thr	Asn	Tyr	Phe	Leu 40	Val	Asn	Leu	Ala	Phe 45	Ser	Asp	Ala
	Ser	Val 50	Ala	Ala	Phe	Asn	Thr 55	Leu	Ile	Asn	Phe	Ile 60	Tyr	Gly	Leu	His
	Ser 65	Glu	Trp	Tyr	Phe	Gly 70	Ala	Asn	Tyr	Cys	Arg 75	Phe	Gln	Asn	Phe	Phe 80
15	Pro	Ile	Thr	Ala	Val 85	Phe	Ala	Ser	Ile	Tyr 90	Ser	Met	Ala	Ile	Ala 95	Val
	Asp	Arg	Tyr	Met 100	Ala	Ile	Ile	Asp	Pro 105	Leu	Lys	Pro	Arg	Leu 110	Ser	Ala
20	Thr	Ala	Thr 115	Lys	Ile	Val	Ile	Gly 120	Ser	Ile	Trp	Ile	Leu 125	Ala	Phe	Leu
	Leu	Ala 130	Phe	Pro	Gln	Cys	Leu 135	Tyr	Ser	Lys	Ile	Leu 140	Gly	Arg	Thr	Leu
	Cys 145	Tyr	Val	Trp	Pro	Glu 150	Gly	Pro	Lys	Gln	His 155	Phe	Thr	Tyr	His	Ile 160
25	Ile	Val	Ile	Ile	Leu 165	Val	Tyr	Cys	Phe	Pro 170	Leu	Leu	Ile	Leu	Thr 175	Tyr
	Thr	Ile	Val	Gly 180	Ile	Thr	Leu	Trp	Gly 185	Gly	Glu	Ile	Pro	Gly 190	Asp	Thr
30	Cys	Asp	Lys 195	Tyr	His	Glu	Gln	Leu 200	Lys	Ala	Lys	Arg	Lys 205	Val	Val	Met
	Asn	Ile 210	Val	Val	Val	Thr	Phe 215	Ala	Ile	Cys	Trp	Leu 220	Pro	Tyr	His	Val
	Tyr 225	Phe	Ile	Leu	Thr	Ala 230	Ile	Tyr	Gln	Gln	Leu 235	Asn	Arg	Trp	Lys	Tyr 240
35	Ile	Gln	Gln	Val	Tyr 245	Leu	Ala	Ser	Phe	Trp 250	Leu	Ala	Met	Ser	Ser 255	Thr
	Met	Tyr	Asn	Pro 260	Ile	Ile	Tyr	Cys	Cys 265	Leu	Asn	Lys	Arg	Phe 270	Arg	Ala
40	Gly	Phe	Lys 275	Arg	Ala	Phe	Arg	Trp 280	Cys	Pro	Phe	Ile	Gln 285	Val	Ser	Ser
	·•	•	~ · .	.	~ 7	-	-	m1 .	~ ; .	•	- ;		,			

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5	(2)	(2) INFORMATION FOR SEQ ID NO:51: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 325 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide															
10		(xi)		JENCI	E DES	- SCRII	TIO	N: SE	_			Val	Val	Gly	Ile	Phe	Gly
		Asn	Ser	Leu	Val 20	Val	Ile	Val	Ile	Tyr 25	Phe	Tyr	Met	Lys	Leu 30	Lys	Thr
		Tyr	Ala	Ser 35	Val	Phe	Leu	Leu	Asn 40	Leu	Ala	Leu	Ala	Asp 45	Leu	Cys	Phe
15		Leu	Leu 50	Thr	Leu	Pro	Leu	Trp 55	Ala	Val	Tyr	Thr	Leu 60	Tyr	Arg	Trp	Pro
		Phe 65	Gly	Asn	Tyr	Leu	Cys 70	Lys	Ile	Ala	Ser	Ala 75	Ser	Val	Ser	Phe	Asn 80
20		Leu	Tyr	Ala	Ser	Val 85	Phe	Leu	Leu	Thr	Cys 90	Leu	Ser	Ile	Asp	Arg 95	Tyr
		Leu	Ala	Ile	Val 100	His	Pro	Met	Lys	Ser 105	Arg	Leu	Arg	Arg	Leu 110	Val	Ala
		Lys	Val	Thr 115	Cys	Ile	Ile	Ile	Trp 120	Leu	Leu	Ala	Gly	Ile 125	Ala	Ser	Leu
25		Pro	Thr 130	Ile	Ile	His	Arg	Asn 135	Phe	Phe	Ile	Glu	Asn 140	Thr	Asn	Ile	Thr
		Val 145	Cys	Ala	Phe	His	Tyr 150	Glu	Ser	Gln	Asn	Ser 155	Thr	Leu	Pro	Val	Gly 160
30		Leu	Gly	Leu	Thr	Lys 165	Asn	Ile	Leu	Gly	Phe 170	Leu	Phe	Pro	Phe	Leu 175	Ile
		Ile	Leu	Thr	Ser 180	Tyr	Thr	Leu	Ile	Trp 185	Lys	Thr	Leu	Lys	Lys 190	Ala	Tyr
		Glu	Ile	Gln 195	Lys	Asn	Lys	Pro	Arg 200	Lys	Asp	Asp	Ile	Phe 205	Lys	Ile	Ile
35		Ile	Ala 210	Ile	Val	Leu	Phe	Phe 215	Phe	Phe	Ser	Trp	Val 220	Pro	His	Asn	Ile
		Phe 225	Thr	Phe	Met	Val	Leu 230	Ile	Gln	Leu	Gly	Leu 235	Ile	Arg	Asp	Cys	Lys 240
40		Ile	Glu	Asp	Ile	Val 245	Asp	Thr	Ala	Met	Pro 250	Ile	Thr	Ile	Cys	Leu 255	Ala
		Tyr	Phe	Gln	Gln 260	Asn	Leu	Asn	Pro	Leu 265	Phe	Tyr	Gly	Phe	Leu 270	Gly	Lys
		Lys	Phe	Lys 275	Lys	Tyr	Phe	Leu	His 280	Ala	Leu	Leu	Lys	Tyr 285	Ile	Pro	Pro
45		Lys	Ala 290	Lys	Ser	His	Ser	Asn 295	Leu	Ser	Thr	Lys	Met 300	Ser	Thr	Leu	Ser

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Tyr Arg Pro Ser Glu Gln Gly Asn Ser Ser Thr Lys Lys Pro Ala Pro 305 310 310 315

		Cys	Ile	Glu	Val	Glu 325											
5	(2)	INFOR	SEQUAL (A) (B) (C) (D)	JENCE LEI TYI STE TOI	E CHA NGTH: PE: 8 RANDE POLOC	ARACT : 282 emino EDNES SY:]	reris 2 am: 5 ac: 5S: s Linea	STICS ino a id sing:	S: acids	5							
		(xi) Ile 1	SEQU Val									Pro	Val	Gly	Phe	Val 15	Glu
15		Asn	Gly	Ile	Leu 20	Leu	Trp	Phe	Leu	Cys 25	Phe	Phe	Thr	Val	Tyr 30	Thr	His
		Leu	Ser	Ile 35	Ala	qaA	Ile	Ser	Leu 40	Leu	Phe	Cys	Ile	Phe 45	Ile	Leu	Ser
20		Ile	Asp 50	Tyr	Ala	Leu	qaA	Tyr 55	Glu	Leu	Ser	Ser	Gly 60	His	Tyr	Tyr	Thr
		Ile 65	Val	Thr	Leu	Ser	Val 70	Thr	Phe	Leu	Phe	Gly 75	Tyr	Asn	Thr	Gly	Leu 80
		Tyr	Leu	Leu	Thr	Ala 85	Ile	Ser	Val	Glu	Arg 90	Cys	Leu	Ser	Val	Leu 95	Tyr
25		Pro	Ile	Trp	Tyr 100	Arg	Cys	His	Arg	Pro 105	Lys	Tyr	Gln	Ser	Ala 110	Leu	Val
		Cys	Ala	Leu 115	Leu	Trp	Ala	Leu	Ser 120	Cys	Leu	Val	Thr	Thr 125	Mec	Tyr	Val
30		Met	Cys 130	Ile	Asp	Arg	Phe	Glu 135	Glu	Ser	His	Ser	Arg 140	Asn	Asp	Cys	Arg
		Ala 145	Val	Ile	Ile	Phe	Ile 150	Ala	Ile	Leu	Ser	Phe 155	Leu	Val	Phe	Thr	Pro 160
		Ser	Val	Ser	Ser	Thr 165	Ile	Leu	Val	Val	Lys 170	Ile	Arg	Lys	Asn	Thr 175	Trp
35		Ala	Ser	His	Ser 180	Ser	Lys	Leu	Tyr	Ile 185	Val	Ile	Met	Val	Thr 190	Ile	Ile
		Ile	Phe	Leu 195	Ile	Phe	Ala	Met	Pro 200	Met	Arg	Leu	Leu	Tyr 205	Leu	Leu	Tyr
40		Tyr	Glu 210	Tyr	Trp	Ser	Thr	Phe 215	Gly	Asn	Leu	His	His 220	Ile	Ser	Leu	Leu
		Phe 225	Ser	Thr	Ile	Asn	Ser 230	Ser	Ala	Asn	Pro	Phe 235	Ile	Tyr	Phe	Phe	Val 240

060 - 065

Cys Asn Thr Val Thr Val Glu Thr Val Val

Howell I was earlier experiences

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5	(2)	INFOI (i)	SEQ((A) (B) (C) (D)	JENCI LEI TYI STI	E CHI NGTH PE: & RANDI POLO(ARACT : 332 amino EDNES SY: 1	reris 2 am: 5 ac: 6S: s lines	STICS ino a id singl	S: acids	5							
10		(xi) Tyr 1										Ile	Asn	Ile	Leu	Ala 15	Ile
		Met	Gly	Asn	Val 20	Met	Thr	Leu	Phe	Val 25	Leu	Leu	Thr	Ser	Arg 30	Tyr	Lys
15		Leu	Thr	Val 35	Pro	Arg	Phe	Ile	Met 40	Asn	Leu	Ser	Phe	Ala 45	Asp	Phe	Cys
		Met	Leu 50	Tyr	Leu	Leu	Leu	Ile 55	Ala	Ser	Val	Asp	Ser 60	Gln	Thr	Lys	Gly
		Gln 65	Tyr	Tyr	Asn	His	Ala 70	Ile	Asp	Trp	Gln	Thr 75	Gly	Ser	Gly	Cys	Ser 80
20		Thr	Ala	Gly	Phe	Phe 85	Thr	Val	Leu	Ala	Ser 90	Glu	Leu	Ser	Val	Tyr 95	Thr
		Leu	Thr	Val	Ile 100	Thr	Leu	Glu	Arg	Trp 105	His	Thr	Ile	Thr	Tyr 110	Ala	Ile
25		His	Ile	Asp 115	Gln	Lys	Leu	Arg	Leu 120	Arg	His	Ala	Ile	Leu 125	Ile	Met	Leu
			130					135					140			Val	_
		Val 145	Ser	Asn	Tyr	Met	Lys 150	Val	Ser	Ile	Cys	Leu 155	Pro	Met	Val	Glu	Thr 160
30		Thr	Leu	Ser	Gln	Val 165	Tyr	Ile	Leu	Thr	Ile 170	Leu	Ile	Leu	Asn	Val 175	Val
		Ala	Phe	Leu	Ile 180	Ile	Cys	Ala	Суѕ	Tyr 185	Ile	Lys	Ile	Tyr	Phe 19	Ala	Val
35				195					200					205		Ala	
			210					215					220			Phe	
		Ala 225	Ile	Ser	Ala	Ala	Phe 230	Lys	Val	Pro	Leu	Ile 235	Val	Thr	Asn	Ser	Lys 240
40		Val	Leu	Leu	Val	Leu 245	Phe	Tyr	Pro	Ile	Asn 250	Ser	Cys	Ala	Asn	Pro 255	Phe
					260					265					270	Ile	
45		Ser	Lys	Phe 275	Cys	Cys	Lys	Arg	Arg 280	Ala	Asp	Ile	Tyr	Arg 285	Arg	Lys	Asp
		Phe	Ser 290	Ala	Tyr	Thr	Ser	Asn 295	Cys	Lys	Lys	Gly	Phe 300	Thr	Gly	Ser	Asn

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Lys Pro Ser Gln Ser Thr Leu Lys Leu Ser Thr Leu His Cys Gln Gly

		Thr	Ala	Leu	Leu	Asp 325	Lys	Arg	Arg	Tyr	Thr 330	Glu	Cys				
5	(2)	INFOR	SEQUAL (A)	ION I JENCI LEI TYI STI	E CHA NGTH: PE: 8	ARACT : 336 umino	reris 5 am: 5 ac:	STICS ino a id	S: acids	5							
10		(ii)	MOLI		E TYI	E: F	ept:	ide									
		(xi)	_						_				_	_	_		_
		1 1	Lys	Phe	Leu	Arg 5	lie	Val	Val	Trp	10	Val	Ser	Leu	Leu	15	Leu
15		Leu	Gly	Asn	Val 20	Phe	Val	Leu	Leu	Ile 25	Leu	Leu	Thr	Ser	His 30	Tyr	Lys
		Leu	Asn	Val 35	Pro	Arg	Phe	Ile	Met 40	Asn	Ile	Ala	Phe	Ala 45	Asp	Phe	Cys
20		Met	Met 50	Tyr	Leu	Leu	Leu	Ile 55	Ala	Ser	Val	Asp	Leu 60	Tyr	Thr	His	Ser
		Glu 65	Tyr	Tyr	Asn	His	Ala 70	Ile	Asp	Trp	Gln	Thr 75	Gly	Pro	Gly	Cys	Asn 80
		Thr	Ala	Gly	Phe	Phe 85	Thr	Val	Phe	Ala	Ser 90	Glu	Leu	Ser	Val	Tyr 95	Thr
25		Leu	Thr	Val	Ile 100	Thr	Leu	Glu	Arg	Trp 105	Tyr	Ala	Ile	Thr	Phe 110	Ala	Met
		Arg	Leu	Asp 115	Arg	Lys	Ile	Arg	Leu 120	Arg	His	Ala	Cys	Ala 125	Ile	Met	Val
30		Gly	Gly 130	Trp	Val	Сув	Сув	Phe 135	Leu	Leu	Ala	Leu	Leu 140	Pro	Leu	Val	Gly
		Ile 145	Ser	Ser	Tyr	Ala	Lys 150	Val	Ser	Ile	Cys	Leu 155	Pro	Met	Thr	Glu	Thr 160
		Pro	Leu	Ala	Leu	Ala 165	Tyr	Ile	Val	Phe	Val 170	Leu	Thr	Leu	Asn	Ile 175	Val
35		Ala	Phe	Val	Ile 180	Val	Cys	Cys	Cys	Tyr 185	Val	Lys	Ile	Tyr	Ile 190	Thr	Val
		Arg	Asn	Pro 195	Gln	Tyr	Asn	Pro	Gly 200	Asp	Lys	Asp	Thr	Lys 205	Ile	Ala	Lys
40		Arg	Met 210	Ala	Val	Leu	Ile	Phe 215	Thr	Asp	Phe	Ile	Cys 220	Met	Ala	Pro	Ile
		Ser 225	Phe	Tyr	Ala	Leu	Ser 230	Ala	Ile	Leu	Asn	Lys 235		Leu	Ile	Thr	Val 240

260 265 270

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		Val	Phe	Ile 275	Leu	Leu	Ser	Lys	Phe 280	Gly	Ile	Cys	Lys	Arg 285	Gln	Ala	Gln
		Ala	Tyr 290	Arg	Gly	Gln	Arg	Val 295	Pro	Pro	Lys	Asn	Ser 300	Thr	Asp	Ile	Gln
5		Val 305	Gln	Lys	Val	Thr	His 310	qaA	Met	Arg	Gln	Gly 315	Ala	Leu	Asn	Met	Glu 320
		Asp	Val	Val	Glu	Leu 325	Ile	Glu	Asn	Ser	His 330	Leu	Thr	Pro	Lys	Lys 335	Gln
10	(2)	INFOF	SEQU (A) (B) (C)	ION E JENCE LEN TYI STE	E CHA NGTH: PE: & RANDE	ARĀCT : 327 :mino :DNES	TERIS 7 ami 5 aci 5S: 8	TICS ino a id singl	S: acida	5							
15		(ii)															
		(xi) Tyr 1	_	JENCI Ile								Ile	Ser	Ile	Leu	Ala 15	Ile
20		Thr	Gly	Asn	Ile 20	Ile	Val	Leu	Val	Ile 25	Leu	Thr	Thr	Ser	Gln 30	Tyr	Lys
		Leu	Thr	Val 35	Pro	Arg	Phe	Leu	Met 40	Asn	Ile	Ala	Phe	Ala 45	qaA	Leu	Cys
		Ile	Gly 50	Ile	Tyr	Leu	Leu	Leu 55	Ile	Ala	Ser	Val	Asp 60	Ile	His	Thr	Lys
25		Ser 65	Gln	Tyr	His	Asn	Tyr 70	Ala	Ile	Asp	Trp	Gln 75	Arg	Gly	Ala	Gly	Cys 80
		Asp	Ala	Ala	Gly	Phe 85	Phe	Thr	Val	Phe	Ala 90	Ser	Glu	Leu	Ser	Val 95	Tyr
30		Thr	Leu	Thr	Ala 100	Ile	Thr	Leu	Glu	Arg 105	Trp	His	Thr	Ile	Thr 110	His	Ile
		Met	Gln	Ile 115	Asp	Сув	Lys	Val	Gln 120	Leu	Arg	His	Ala	Ala 125	Ser	Val	Met
		Val	Met 130	Gly	Trp	Ile	Phe	Ala 135	Phe	Ala	Ala	Ala	Leu 140	Phe	Pro	Ile	Phe
35		Gly 1 4 5	Ile	Ser	Ser	Tyr	Met 150	Lys	Val	Ser	Ile	Cys 155	Leu	Pro	Leu	Ile	Asp 160
				Leu		165					170					175	
40		Leu	Ala	Phe	Val 180	Val	Ile	Cys	Gly	Cys 185	Tyr	Thr	His	Ile	Tyr 19u	Leu	Thr
		Val	Arg	Asn 195	Pro	Asn	Ile	Val	Ser 200	Ser	Ser	Ser	Asp	Thr 205	Arg	Ile	Ala
		Lys	Arg 210	Met	Leu	Ile	Phe	Thr 215	Asp	Phe	Leu	Leu	Pro 220	Ile	Ser	Phe	Phe
45		Ala 225	Ile	Ser	Ala	Ser	Leu 230	Lys	Val	Pro	Leu	Ile 235	Thr	Val	Ser	Lys	Ala 240
		Lys	Ile	Leu	Leu	Val	Leu	Phe	His	Pro	Ile	Asn	Ser	Cys	Ala	Asn	Pro

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						245					250					255	
		Phe	Leu	Tyr	Ala 260	Ile	Phe	Thr	Lys	Asn 265	Phe	Arg	Arg	Asp	Phe 270	Phe	Ile
5		Leu	Leu	Ser 275	Lys	Cys	Gly	Cys	Tyr 280	Glu	Met	Gln	Ala	Gln 285	Ile	Tyr	Arg
		Thr	Glu 290	Thr	Ser	Ser	Thr	Val 295	His	Asn	Thr	Hıs	Pro 300	Arg	Asn	Gly	His
		Cys 305	Ser	Ser	Ala	Pro	Arg 310	Val	Thr	Ser	Gly	Ser 315	Ser	Arg	Tyr	Ile	Leu 320
10		Val	Pro	Leu	Ser	Leu 325	Gln	Asn									
15	(2)	(ii)	SEQU (A) (B) (C) (D)	JENCE LEN TYE STE	CHANGTH: PE: & RANDI POLOG	ARACT : 309 amino EDNES SY:	reris ami aci ss: s linea	STICS ino a id singl	S: acids	5							
20		(xi) Ser 1	SEQU Met	JENCI Leu	E DES Ala	SCRII Ala 5	PTIOI Tyr	N: SI Met	EQ II Phe	NO Leu	:56: Leu 10	Ile	Val	Leu	Gly	Phe 15	Pro
		Ile	Asn	Phe	Leu 20	Thr	Leu	Tyr	Val	Thr 25	Val	Gln	His	Lys	Lys 30	Leu	Arg
25		Thr	Pro	Ile 35	Asn	Tyr	Ile	Leu	Leu 40	Asn	Leu	Ala	Val	Ala 45	Asp	Leu	Phe
		Met	Val 50	Leu	Gly	Gly	Phe	Thr 55	Ser	Thr	Leu	Tyr	Thr 60	Ser	Leu	His	Gly
		Tyr 65	Phe	Val	Phe	Gly	Pro 70	Thr	Gly	Cys	Asn	Leu 75	Glu	Gly	Phe	Phe	Ala 80
30		Thr	Leu	Gly	Gly	Clu 85	Ile	Ala	Leu	Trp	Ser 90	Leu	Trp	Leu	Ala	Ile 95	Glu
		Arg	Tyr	Val	Val 100		Cys	Lys	Pro	Met 105	Ser	Asn	Phe	Arg	Phe 110	Gly	Glu
35		Asn	His	Ala 115	Ile	Met	Gly	Val	Ala 120		Thr	Trp	Val	Met 125		Leu	Ala
		Cys	Ala 130		Pro	Pro	Ile	Ala 135		Trp	Ser	Arg	Tyr 140		Pro	Glu	Gly
		Leu 145		Cys	Ser	Cys	Gly 150		Asp	Tyr	Tyr	Thr 155	Leu	Lys	Pro	Glu	Val 160
40		Asn	Asn	Glu	Ser	Phe		Ile	Tyr	Met	Phe 170		Val	His	Phe	Thr 175	Ile
		Pro	Leu	Ile	Ile	Phe	Phe	e Cys	Tyr	Gly		Leu	Val	. Phe	Thr	. Val	Lys
		Lys	5 Glu 210		Thr	: Arg	; Met	. Va. 215		e lle	- Met	. Va.	. 11e 220	a Ala	i Pho	iev	1.6

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	Cys 225		Val	Pro	Tyr	Ala 230	Ser	Val	Ala	Phe	Tyr 235	Ile	Phe	Thr	His	Gln 240
	Gly	Ser	Asn	Phe	Gly 245	Pro	Ile	Phe	Met	Arg 250	Ile	Pro	Ala	Phe	Phe 255	Ala
5	Lys	Ser	Ala	Ala 260	Ile	Tyr	Asn	Pro	Val 265	Ile	Tyr	Ile	Ile	Phe 270	Asn	Lys
	Gln	Phe	Arg 275	Asn	Cys	Met	Leu	Gln 280	Leu	Ile	Cys	Cys	Gly 285	Lys	Asn	Pro
10	Leu	Gly 290	Asp	Asp	Glu	Ala	Ser 295	Ala	Thr	Val	Ser	Lys 300	Arg	Glu	Thr	Ser
	Gln 305	Val	Ala	Pro	Ala											
15	(2) INFO: (i)	SEQI (A (B (C (D	UENCI LEI TYI STI	E CHI NGTH PE: & RANDI POLO	ARAC: 29 mino EDNES	reris 7 am: 5 ac: 5S: s lines	STICS ino a id sing: ar	S: acida	5							
20	(xi) Met 1	SEQ:	JENCI Phe	E DES Val	SCRII Val 5	PTION Ile	N: SI Ala	EQ II Ser	NO Val	:57: Phe 10	Thr	Asn	Gly	Leu	Val 15	Leu
	Ala	Ala	Thr	Met 20	Lys	Phe	Lys	Lys	Leu 25	Pro	His	Pro	Ile	Asn 30	Trp	Ile
25	Leu	Val	Asn 35	Leu	Ala	Val	Ala	Asp 40	Ile	Ala	Gly	Thr	Val 45	Ile	Ala	Ser
	Thr	Ile 50	Ser	Val	Val	Asn	Gln 55	Val	Tyr	Gly	Tyr	Phe 60	Val	Leu	Gly	His
30	Pro 65	Met	Cys	Val	Leu	Glu 70	Gly	Tyr	Thr	Val	Ser 75	Leu	Cys	Gly	Ile	Thr 80
	Gly	Leu	Trp	Ser	Leu 85	Ala	Ile	Ile	Ser	Trp 90	Glu	Arg	Trp	Met	Val 95	Val
	Cys	Lys	Pro	Phe 100	Gly	Asn	Val	Arg	Phe 105	Asp	Ala	Lys	Ile	Ala 110	Ile	Val
35	Gly	Ile	Ala 115	Phe	Ser	Trp	Ile	Trp 120	Ala	Ala	Val	Trp	Thr 125	Ala	Pro	Pro
	Ile	Phe 130	Gly	Trp	Ser	Arg	Tyr 135	Trp	Pro	His	Gly	Leu 140	Lys	Thr	Ser	Cys
40	Gly 145	Pro	Asp	Val	Phe	Ser 150	Gly	Ser	Ser	Tyr	Pro 155	Gly	Val	Gln	Ser	Leu 160
	Leu	Cys	Ile	Thr	Pro 165	Leu	Ser	Ile	Ile	Val 170	Leu	Cys	Tyr	Leu	Gln 175	Val
	Trp	Thr	Ala	Ile 180	Arg	Ala	Val	Ala	Lys 185	Gln	Gln	Lys	Glu	Ser 190	Glu	Ser
45	Thr	Gln	Lys 195	Ala	Glu	Lys	Glu	Val 200	Thr	Arg	Met	Trp	Val 205	Met	Val	Leu
	Ala	Phe	Cys	Phe	Cys	Trp	Gly	Pro	Tyr	Ala	Phe	Phe	Ala	Cys	Phe	Ala

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											_						
			210					215					220				
		Ala 225	Ala	Asn	Pro	Gly	Tyr 230	Pro	Phe	His	Pro	Leu 235	Met	Ala	Ala	Leu	Pro 240
5		Ala	Phe	Phe	Ala	Lys 345	Ser	Ala	Thr	Ile	Tyr 250	Asn	Pro	Val	Ile	Tyr 255	Val
		Phe	Met	Asn	Arg 260	Gln	Phe	Arg	Asn	Cys 265	Ile	Leu	Gln	Leu	Phe 270	Gly	Lys
		Lys	Val	Asp 275	Asp	Gly	Ser	Glu	Leu 280	Ser	Ser	Ala	Ser	Lys 285	Thr	Glu	Val
10		Ser	Ser 290	Val	Ser	Ser	Val	Ser 295	Pro	Ala							
15	(2)	INFOI (i)	SEQU (A) (B) (C) (D)	JENCI LEI TYI STI	E CHI NGTH PE: 6 RANDI POLO	ARACT 29 mino EDNES GY:	reris 7 am: 5 ac: 5S: s linea	STICS ino a id sing: ar	S: acid:	5							
20		(xi) Arg 1	SEQ1 Cys	JENCI Phe	E DE: Val	SCRII Val 5	PTIOI Thr	N: SI Ala	EQ II Ser	NO Val	:58: Phe 10	Thr	Asn	Gly	Leu	Val 15	Leu
		Ala	Ala	Thr	Met 20	Lys	Phe	Lys	Lys	Leu 25	Arg	His	Pro	Leu	Asn 30	Trp	Ile
25		Leu	Val	Asn 35	Ile	Ala	Val	Ala	Asp 40	Ile	Ala	Gly	Thr	Val 45	Ile	Ala	Ser
		Thr	Ile 50	Ser	Ile	Val	Asn	Gln 55	Val	Ser	Gly	Tyr	Phe 60	Val	Leu	Gly	His
		Pro 65	Met	Cys	Val	Leu	Glu 70	Gly	Tyr	Thr	Val	Ser 75	Leu	Cys	Gly	Ile	Thr 80
30		Gly	Leu	Trp	Ser	Leu 85	Ala	Ile	Ile	Ser	Trp 90	Glu	Arg	Trp	Leu	Trp 95	Cys
		Lys	Pro	Phe	Gly 100	Asn	Val	Arg	Phe	Asp 105	Ala	Lys	Ile	Ala	Ile 110	Val	Gly
35		Ile	Ala	Phe 115		Trp	Ile	Trp	Ser 120		Val	Trp	Thr	Ala 125	Pro	Pro	Ile
		Phe	Gly 130		Ser	Arg	Tyr	Trp 135		His	Gly	Leu	Lys 140		Ser	Cys	Gly
		Pro 145		Val	Phe	Ser	Gly 150		Ser	Tyr	Pro	Gly 155		Gln	Ser	Leu	Val 160
40		Ile	Met	Val	Thr	Cys 165		Ile	: Ile	Pro	170		lle	Ile	. Leu	Cys 175	
		Leu	ı Glm	. Val	Tr	Let	Ala	ı Ile	e Arg	, Ala	. Val	. Ala	Lys	Glr	n Glm	Lys	; Glu

Ala Tyr Cys Val Cys Trp Gly Pro Tyr Thr Phe Phe Ala Cys Phe Ala 210 215 220 WO 94/05695 PCT/US93/08528

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	Ala 225	Ala	Asn	Pro	Gly	Tyr 230	Ala	Phe	His	Pro	Leu 235	Met	Ala	Ala	Leu	Pro 240
	Ala	Tyr	Phe	Ala	Lys 2 4 5	Ser	Ala	Thr	Ile	Tyr 250	Asn	Pro	Val	Ile	Tyr 255	Val
5	Phe	Met	Asn	Arg 260	Gln	Phe	Arg	Asn	Cys 265	Ile	Leu	Gln	Leu	Phe 270	Gly	Lys
	Lys	Val	Asp 275	Asp	Gly	Ser	Glu	Leu 280	Ser	Ser	Ala	Ser	Lys 285	Thr	Glu	Val
10	Ser	Ser 290	Val	Ser	Ser	Val	Ser 295	Pro	Ala							
	(2) INFOI (i)	SEQ	JENCI LEI	E CHI NGTH		reris	STICS ino a	S :	5							
15	(ii)		TOI	POLO	EDNES SY: 1 PE: p	linea	ar	le								
20	(xi) Gln 1	SEQT Ala									Ile	Gly	Phe	Pro	Leu 15	Leu
	Val	Ala	Thr	Leu 20	Ala	Tyr	Lys	Lys	Leu 25	Arg	Gln	Pro	Asn	Tyr 30	Ile	Leu
	Val	Asn	Val 35	Ser	Phe	Gly	Gly	Phe 40	Leu	Leu	Cys	Ile	Phe 45	Ser	Val	Phe
25	Pro	Val 50	Phe	Val	Ala	Ser	Сув 55	Asn	Gly	Tyr	Phe	Val 60	Phe	Gly	Arg	His
	Val 65	Сув	Ala	Leu	Glu	Gly 70	Phe	Leu	Gly	Thr	Val 75	Ala	Gly	Leu	Val	Thr 80
30	Gly	Trp	Ser	Leu	Ala 85	Phe	Leu	Ala	Phe	Glu 90	Arg	Tyr	Ile	Val	Ile 95	Cys
	Lys	Pro	Phe	Gly 100	Asn	Phe	Arg	Phe	Ser 105	Ser	Lys	His	Ala	Leu 110	Thr	Val
	Val	Ile	Ala 115	Thr	Trp	Thr	Ile	Gly 120	Ile	Gly	Val	Ser	Ile 125	Pro	Pro	Phe
35	Phe	Gly 130	Trp	Ser	Arg	Phe	Ile 135	Pro	Glu	Gly	Leu	Gln 140	Cys	Ser	Cys	Gly
	Pro 145	Asp	Lys	Tyr	Thr	Val 150	Gly	Thr	Lys	Tyr	Arg 155	Ser	Glu	Ser	Tyr	Thr 160
40	Trp	Phe	Leu	Phe	Ile 165	Phe	Cys	Phe	Ile	Val 170	Pro	Leu	Ser	Leu	Ile 175	Cys
	Phe	Ser	Tyr	Thr 180	Gln	Leu	Leu	Arg	Ala 185	Leu	Lys	Ala	Val	Ala 190	Ala	Gln
	Gln	Gln	Glu 195	Ser	Ala	Thr	Thr	Gln 200	Lys	Ala	Glu	Arg	Glu 205	Val	Ser	Arg
45	Met	Val 210	Val	Val	Met	Val	Gly 215	Ser	Phe	Cys	Val	Cys 220	Tyr	Val	Pro	Tyr
	Ala	Ala	Phe	Ala	Met	Tyr	Met	Val	Asn	Asn	Arg	Asn	His	Gly	Leu	Asp

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	225					230					235					240
	Leu	Arg	Leu	Val	Arg 245	Ile	Pro	Ser	Phe	Phe 250	Ser	Lys	Ser	Ala	Cys 255	Ile
5	Tyr	Asn	Pro	Ile 260	Ile	Tyr	Cys	Phe	Met 265	Asn	Lys	Gln	Phe	Gln 270	Ala	Cys
	Ile	Met	Met 275	Val	Cys	Gly	Lys	Ala 280	Met	Met	Glu	Ser	Asp 285	Thr	Cys	Ser
	Ser	Gln 290	Lys	Thr	Glu	Val	Ser 295	Thr	Val	Ser	Ser	Thr 300	Gln	Val	Gly	Pro
10	Asn 305															
15	(2) INFOR (i)	SEQU (A) (B) (C) (D)	JENCE LEN TYI STI TOI	E CHA NGTH: PE: & RANDI POLO	ARACT 293 amino SDNES 3Y:	reris 3 am: 5 ac: 5S: 8 linea	STICS ino a id sing:	S: acida	5							
20	(xi) Leu 1		JENCI Tyr								Leu	Val	Thr	Val	Ile 15	Gly
	Asn	Ile	Ser	Ile 20	Ile	Val	Ala	Ile	Ile 25	Ser	Asp	Pro	Cys	Leu 30	His	Thr
25	Pro	Met	Tyr 35	Phe	Phe	Leu	Ser	Asn 40	Leu	Ser	Phe	Val	Asp 45	Ile	Cys	Phe
	Ile	Ser 50	Thr	Thr	Val	Pro	Val 55	Asn	Thr	Gln	Thr	Gln 60	Asn	Asn	Val	Ile
	Thr 65	Tyr	Ala	Gly	Сув	Ile 70	Thr	Gln	Ile	Tyr	Phe 75	Phe	Leu	Leu	Phe	Val 80
30	Glu	Leu	Asp	Asn	Phe 85	Leu	Leu	Thr	Ile	Met 90	Ala	Tyr	Asp	Arg	Tyr 95	Val
	Ala	Ile	Сув	His 100	Pro	Met	His	Tyr	Thr 105	Val	Ile	Met	Asn	Tyr 110	Lys	Leu
35	Cys	Gly	Phe 115	Leu	Val	Leu	Val	Ser 120	Trp	Ile	Val	Ser	Val 125	Leu	His	Ala
	Leu	Phe 130	Gln	Ser	Leu	Ala	Leu 135	Pro	Phe	Cys	Thr	His 140	Leu	Glu	Ile	Pro
	His 145	_	Phe	Cys	Glu	Pro 150	Asn	Gln	Val	Ile	Gln 155	Leu	Thr	Cys	Ser	Asp 160
40	Ala	Phe	Leu	Asn	Asp 165	Leu	Val	Ile	Tyr	Phe 170	Thr	Leu	Val	Leu	Leu 175	Ala
	Thr	Val	Pro	Ile	Ala	Gly	Ile	Phe	Tyr	Ser	Tyr	Phe	Ala	Ile	Ser	Ser

Val Val Ser Leu Phe Tyr Cys Thr Gly Leu Gly Val Tyr Leu Ser Ser 210 215

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										~ -	Ū						
		Ala 225	Ala	Asn	Asn	Ser	Leu 230	Ser	Ala	Thr	Ala	Ser 235	Val	Met	Tyr	Thr	Val 240
		Val	Thr	Pro	Met	Val 245	Asn	Pro	Phe	Ile	Tyr 250	Ser	Leu	Arg	Asn	Lys 255	Asp
5		Val	Lys	Ser	Val 260	Leu	Lys	Lys	Thr	Leu 265	Cys	Glu	Glu	Val	Ile 270	Arg	Ser
		Pro	Pro	Ser 275	Leu	Leu	His	Phe	Phe 280	Leu	Val	Leu	Cys	His 285	Leu	Pro	Cys
10		Phe	Ile 290	Phe	Cys	Tyr											
15	(2)	INFOR	SEQUAL (A) (B) (C) (D)	JENCE LEN TYI STI TOI	CHI NGTH PE: 8 RANDI POLO	ARACT : 284 emino EDNES GY:	reris 1 ami 5 aci 5S: s linea	STICS ino a id singl	S: acids	5							
20		(xi) Leu 1	SEQU Leu									Leu	Ala	Thr	Val	Leu 15	Gly
		Asn	Leu	Leu	Ile 20	Ile	Leu	Ala	Ile	Gly 25	Gly	Asp	Ser	Arg	Leu 30	His	Thr
		Pro	Met	Tyr 35	Phe	Phe	Leu	Ser	Asn 40	Leu	Ser	Phe	Val	Asp 45	Val	Cys	Phe
25		Ser	Ser 50	Thr	Thr	Val	Pro	Lys 55	Val	Leu	Ala	Asn	His 60	Ile	Leu	Gly	Ser
		Gln 65	Ala	Ile	Ser	Phe	Ser 70	Gly	Cys	Leu	Thr	Gln 75	Leu	Tyr	Phe	Leu	Ala 80
30		Val	Phe	Gly	Asn	Met 85	Asp	Asn	Phe	Leu	Leu 90	Ala	Val	Met	Ser	Tyr 95	Asp
		Arg	Tyr	Val	Ala 100	Ile	Cys	His	Pro	Leu 105	His	Tyr	Thr	Thr	Ile 110	Arg	Gln
		Leu	Cys	Val 115	Leu	Leu	Val	Val	Gly 120	Ser	Trp	Val	Val	Ala 125	Asn	Met	Asn
35		Cys	Leu 130	Leu	His	Ile	Leu	Ile 135	Met	Ala	Arg	Lys	Ser 140	Phe	Сув	Ala	Asp
		Leu 145	Pro	His	Phe	Phe	Cys 150	_	Gly	Thr	Pro	Leu 155	Leu	Lys	Leu	Ser	Cys 160
40		Ser	Asp	Thr	His	Leu 165	Asn	Glu	Leu	Met	Ile 170	Leu	Thr	Glu	Gly	Ala 175	Val
		Val	Met	Val	Thr 180		Phe	Val	Cys	Ile 185	Leu	Ile	Ser	Tyr	Ile 190	His	Ile
		Thr	Cys	Ala 195	Val	Leu	Arg	Val	Ser 200		Pro	Arg	Gly	Gly 205	Trp	Lys	Ser
45		Phe	Ser 210	Thr	Cys	Cly	Ser	His 215		Ala	Val	Val	Cys 220		Phe	Tyr	Gly
		Thr	Val	Ile	Ala	Val	Tyr	Phe	Asn	Pro	Ser	Ser	Ser	His	Leu	Ala	Gly

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	225					230					235					240
	Arg	Asp	Met	Ala	Ala 245	Ala	Val	Met	Tyr	Ala 250	Val	Val	Thr	Pro	Met 255	Ile
5	Asn	Pro	Phe	Ile 260	Tyr	Ser	Leu	Arg	Asn 265	Ser	Asp	Met	Lys	Ala 270	Ala	Leu
	Arg	Lys	Val 275	Leu	Ala	Met	Arg	Phe 280	Pro	Ser	Lys	Gln				
10	(ii)	SEQU (A) (B) (C) (D)	JENCE LEN TYE STE TOE	CHA IGTH: PE: & RANDE POLOC	RACT 277 mino EDNES SY:]	TERIS 7 ami 5 aci 3S: 8 Linea	STICS ino a id singl	S: acids	5							
15	(xi)	SEQU	JENCE	E DES	CRIE	PTION	N: SI	EQ II	NO:	62:						
	Leu 1	Leu	Phe	Leu	Leu 5	Phe	Leu	Val	Met	Tyr 10	Leu	Leu	Thr	Val	Val 15	Gly
	Asn	Leu	Ala	Ile 20	Ile	Ser	Leu	Val	Gly 25	Ala	His	Arg	Сув	Leu 30	Gln	Pro
20	His	Thr	Pro 35	Met	Tyr	Phe	Phe	Leu 40	Cys	Asn	Leu	Ser	Phe 45	Leu	Glu	Ile
	Trp	Phe 50	Thr	Thr	Ala	Cys	Val 55	Pro	Lys	Thr	Leu	Ala 60	Thr	Phe	Ala	Pro
25	Arg 65	Gly	Gly	Val	Ile	Ser 70	Leu	Ala	Gly	Cys	Ala 75	Thr	Lys	Tyr	Phe	Val 80
	Phe	Ser	Leu	Gly	Сув 85	Thr	Glu	Tyr	Phe	Leu 90	Leu	Ala	Val	Met	Ala 95	Tyr
	Asp	Arg	Tyr	Leu 100	Ala	Ile	Cys	Leu	Pro 105	Leu	Arg	Tyr	Gly	Gly 110	Ile	Met
30	Arg	Pro	Gly 115	Ile	Ala	Met	Arg	Leu 120	Ala	Leu	Gly	Ser	Trp 125	Leu	Cys	Gly
	Phe	Ser 130	Ala	Ile	Thr	Val	Pro 135	Ala	Thr	Leu	Ile	Ala 140	Arg	Leu	Ser	Phe
35	Cys 145	Gly	Ser	Arg	Val	Ile 150		His	Phe	Phe	Cys 155	Asp	Ile	Ser	Pro	Trp 160
	Ile	Val	Leu	Ser	Сув 165	Thr	Asp	Thr	Gln	Val 170	Val	Glu	Leu	Val	Ser 175	Phe
	Gly	Ile	Ala	Phe 180	Cys	Val	Ile	Leu	Gly 185	Ser	Cys	Gly	Ile	Thr 190	Leu	Val
40	Ser	Tyr	Ala 195	Lys	Ile	Pro	Ser	Ala 200		Gly	Arg	His	Arg 205		Phe	Ser

Lys Ala Ile Thr Val Leu Asn Thr Ile Val Thr Pro Val Leu Asn Pro

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					245					250					255	
	Phe	Ile	Tyr	Thr 260	Leu	Arg	Asn	Lys	Asp 265	Val	Lys	Glu	Ala	Leu 270	Arg	Arg
5	Thr	Val	Lys 275	Gly	Lys											
10	(i)	(B)	JENCE LEN TYE STE TOE	E CHA NGTH: PE: & RANDI POLOC	ARACT : 273 amino EDNES SY: 1	reris 3 ami 5 aci 5S: s linea	STICS ino a id singl	S: acids	5							
15		SEQU Ile									Leu	Val	Thr	Val	Leu 15	Gly
	Asn	Leu	Leu	Ile 20	Ile	Met	Ala	Ile	Ile 25	Thr	Gln	Ser	His	Leu 30	His	Thr
	Pro	Met	Tyr 35	Phe	Phe	Leu	Ser	Phe 40	Val	Asp	Ile	Cys	Phe 45	Thr	Ser	Thr
20	Thr	Ile 50	Pro	Leu	Val	Asn	Ile 55	Tyr	Thr	Gln	Ser	Lys 60	Ser	Ile	Thr	Tyr
	Glu 65	Asp	Cys	Ile	Ser	Leu 70	Val	Phe	Ala	Glu	Leu 75	Gly	Asn	Phe	Leu	Leu 80
25	Ala	Val	Met	Ala	Tyr 85	Asp	Arg	Tyr	Val	Ala 90	Xaa	Cys	His	Pro	Leu 95	Суѕ
	Tyr	Thr	Val	Ile 100	Val	Asn	His	Arg	Leu 105	Cys	Ile	Leu	Leu	Le: 110	Leu	Leu
	Ser	Trp	Val 115	Ile	Ser	Ile	Phe	Arg 120	Ala	Phe	Ile	Gln	Ser 125	Leu	Ile	Val
30	Leu	Gln 130	Leu	Thr	Phe	Cys	Gly 135	Asp	Val	Lys	Ile	Pro 140	His	Phe	Phe	Cys
	Glu 1 4 5	Leu	Asn	Gln	Leu	Ser 150	Gln	Leu	Thr	Cys	Ser 155	Asp	Asn	Phe	Pro	Ser 160
35	His	Leu	Ile	Met	Asn 165	Leu	Val	Pro	Val	Me t 170	Leu	Ala	Ala	Ile	Ser 175	Phe
	Ser	Gly	Ile	Leu 180	Tyr	Ser	Tyr	Phe	Ser 185	Ile	Ser	Thr	Val	Gln 190	Gly	Lys
	Tyr	Lys	Ala 195	Phe	Ser	Thr	Cys	Ala 200	Ser	His	Leu	Ser	Ile 205	Val	Ser	Leu
40	Phe	Tyr 210	Ser	Thr	Gly	Leu	Gly 215	Val	Tyr	Val	Ser	Ser 220	Ala	Val	Val	Gln
	Ser 225	Ser	His	Ser	Ala	Ala 230	Ser	Ala	Ser	Val	Met 235	Tyr	Thr	Val	Val	Pro 240
45	Met	Leu	Asn	Pro	Phe 245	Ile	Tyr	Ser	Leu	Arg 250	Asn	Lys	Asp	Val.	Lys 255	Arg
	Ala	Leu	Glu	Arg 260	Leu	Leu	Glu	Gly	Asn 265	Cys	Lys	Val	His	His 270	Trp	Thr

Gly

(2) INFORMATION FOR SEQ ID NO:64:

5	(ii)	(A) (B) (C) (D)	LEN TYP STP TOP	GTH: PE: & RANDE POLOG TYPE	269 umino IDNES Y: 1	ami aci SS: s linea	ino a id singl	cids	3							
10	(xi) Leu 1			E DES Ala							Leu	Thr	Thr	Ile	Leu 15	Gly
	Asn	Leu	Leu	Ile 20	Ile	Val	Leu	Val	Gln 25	Leu	Asp	Ser	Gln	Leu 30	His	Thr
15	Pro	Met	Tyr 35	Leu	Phe	Leu	Ser	Asn 40	Leu	Ser	Phe	Ser	Asp 45	Leu	Cys	Phe
	Ser	Ser 50	Leu	Lys	Leu	Leu	Gln 55	Asn	Met	Arg	Ser	Gln 60	Asp	Thr	Ser	Ile
20	Pro 65	Tyr	Gly	Gly	Сув	Leu 70	Ala	Gln	Thr	Tyr	Phe 75	Phe	Met	Val	Phe	Gly 80
	Asp	Leu	Ser	Phe	Leu 85	Leu	Val	Ala	Met	Ala 90	Tyr	Asp	Arg	Tyr	Val 95	Ala
	Ile	Cys	Phe	Leu 100	Pro	His	Tyr	Thr	Ser 105	Ile	Met	Ser	Pro	Lys 110	Leu	Cys
25	Thr	Cys	Leu 115	Val	Leu	Leu	Leu	Trp 120	Met	Leu	Thr	Thr	Ser 125	His	Met	Met
	Thr	Leu 130	Leu	Ala	Ala	Arg	Leu 135	Ser	Phe	Cys	Glu	Asn 140	Asn	Trp	Leu	Asn
30	Phe 145	Phe	Cys	Asp	Leu	Phe 150	Val	Leu	Leu	Lys	Ile 155	Ala	Cys	Ser	Asp	Thr 160
	Tyr	Ile	Asn	Glu	Leu 165	Phe	Ile	Met	Ser	Thr 170	Leu	Leu	Ile	Ile	Ile 175	Pro
	Phe	Phe	Leu	Ile 180	Val	Met	Ser	Tyr	Ala 185	Lys	Val	Pro	Ser	Thr 19ù	Gln	Gly
35	Ile	Cys	Lys 195	Val	Phe	Ser	Thr	Cys 200	Gly	Ser	Hıs	Leu	Ser 205	Val	Val	Ser
	Leu	Phe 210	Tyr	Gly	Thr	Ile	Ile 215	Gly	Leu	Tyr	Leu	Cys 220	Pro	Ala	Gly	Asn
40	Asn 225	Ser	Thr	Val	Lys	Glu 230	Met	Val	Met	Ala	Met 235	Met	Tyr	Thr	Val	Val 240
	Thr	Pro	Met	Ile	Asn 245	Pro	Phe	Ile	Tyr	Ser 250	Leu	Arg	Asn	Arg	Asp 255	Leu

TOUTNOS (WARROMERIOMA)

(A) LENGTH: 286 amino acids
(B) TYPE: amino acid

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	(ii)	(D) STI) TOI ECULI	POLO	GY: 3	linea	ar	le								
5	(xi) Leu		UENCI Phe								Val	Leu	Val	Leu	Thr	Glu
	1		Leu	Ile	5				Arg	10				Leu	15	
	Pro	Met	Tyr	20 Phe	Phe	Leu	Phe	Leu	25 Glu	Tle	TTD	Tvr	Val	30 Thr	Val	Thr
10			35					40			-	-	45			
	Ile	Pro 50	Lys	Leu	Met	Gly	Phe 55	Ile	Gly	Ser	Lys	Glu 60	Asn	His	Gly	Gln
	Leu 65	Ile	Ser	Phe	Phe	Ala 70	Сув	Met	Thr	Gln	Leu 75	Tyr	Phe	Phe	Leu	Gly 80
15	Leu	Gly	Cys	Thr	Glu 85	Cys	Val	Leu	Leu	Ala 90	Val	Met	Ala	Туг	Asp 95	Arg
	Tyr	Val	Ala	Ile 100	Сув	His	Pro	Leu	His 105	Tyr	Pro	Val	Ile	Val 110	Ser	Ser
20	Arg	Ile	Glx 115	Val	Leu	Gly	Ser	Trp 120	Ala	Gly	Gly	Phe	Gly 125	Ile	Ser	Met
	Val	Lys 130	Val	Phe	Leu	Ile	Ser 135	Arg	Leu	Ser	Tyr	Cys 140	Gly	Pro	Asn	Thr
	Ile 145	Asn	His	Phe	Phe	Cys 150	Asp	Val	Ser	Pro	Leu 155	Leu	Asn	Leu	Ser	Cys 160
25	Thr	Asp	Met	Ser	Thr 165	Ala	Glu	Leu	Thr	Asp 170	Phe	Val	Ile	Ala	Ile 175	Phe
	Ile	Leu	Leu	Gly 180	Pro	Leu	Ser	Val	Thr 185	Gly	Ala	Ser	Tyr	Met 190	Arg	Ile
30	Pro	Ser	Ala 195	Ala	Gly	Arg	His	Lys 200	Ala	Phe	Ser	Thr	Cys 205	Ala	Ser	His
	Leu	Thr 210	Val	Val	Ile	Ile	Phe 215	Tyr	Ala	Ala	Ser	Ile 220	Phe	Ile	Tyr	Ala
	Arg 225	Pro	Lys	Ala	Leu	Ser 230	Ala	Phe	Thr	qaA	Asn 235	Lys	Leu	Va.l.	Ser	Val 240
35	Leu	Tyr	Ala	Val	11e 245	Val	Pro	Leu	Phe	Asn 250	Pro	Ile	Ile	Tyr	Cys 255	Leu
	Arg	Asn	Gln	Asp 260	Val	Lys	Arg	Ala	Leu 265	Arg	Arg	Thr	Leu	His 270	Leu	Ala
40	Gln	Asp	Gln 275	Glu	Ala	Asn	Thr	Asn 280	Lys	Gly	Ser	Lys	Ile 285	Gly		

(2) INFORMATION FOR SEQ ID NO:66:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 275 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

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	(xi) Leu 1			E DES Ala							Leu	Thr	Thr	Phe	Leu 15	Gly
5	Asn	Leu	Leu	Ile 20	Val	Val	Leu	Val	Gln 25	Leu	Asp	Ser	His	Leu 30	His	Thr
	Pro	Met	Tyr 35	Leu	Phe	Leu	Ser	Asn 40	Leu	Ser	Phe	Ser	As p 45	Leu	Cys	Phe
	Ser	Ser 50	Val	Thr	Met	Leu	Lys 55	Leu	Leu	Gln	Asn	Ile 60	Gln	Ser	Gln	Val
10	Pro 65	Ser	Ile	Ser	Tyr	Ala 70	Gly	Сув	Leu	Trp	Ile 75	Phe	Phe	Phe	Leu	Leu 80
	Phe	Gly	Tyr	Leu	Gly 85	Asn	Phe	Leu	Leu	Val 90	Ala	Met	Ala	Tyr	Asp 95	Arg
15	Tyr	Val	Ala	Ile 100	Cys	Phe	Pro	Leu	His 105	Tyr	Thr	Asn	Ile	Met 110	Ser	His
	Lys	Leu	Cys 115	Thr	Cys	Leu	Leu	Leu 120	Val	Phe	Trp	Ile	Met 125	Arg	Ser	Ser
	His	Ala 130	Met	Met	Ile	Thr	Leu 135	Ile	Ala	Ala	Arg	Leu 140	Ser	Phe	Cys	Glu
20	Asn 145	Asn	Val	Leu	Leu	Asn 150	Phe	Phe	Cys	Asp	Leu 155	Phe	Val	Leu	Leu	Lys 160
	Leu	Ala	Сув	Ser	Asp 165	Thr	Tyr	Val	Asn	Glu 170	Leu	Met	Ile	His	Ile 175	Met
25	Glu	Val	Ile	Ile 180	Ile	Val	Ile	Pro	Phe 185	Val	Leu	Ile	Val	Ile 190	Ser	Tyr
	Ala	Lys	Val 195	Pro	Ser	Thr	Gln	Ser 200	Ile	His	Lys	Val	Phe 205	Ser	Thr	Cys
	Gly	Ser 210	His	Leu	Ser	Val	Val 215	Ser	Leu	Phe	Tyr	Gly 220	Thr	Ile	Ile	Gly
30	Leu 225	Tyr	Leu	Cys	Pro	Ser 230	Gly	qaA	Asn	Phe	Ser 235	Leu	Lys	Gly	Ser	Leu 240
	Thr	Val	Val	Thr	Pro 245	Ile	Met	Pro	Phe	Ile 250	Tyr	Ser	Leu	Arg	Asn 255	Arg
35	Asp	Met	Lys	Gln 260	Ala	Leu	Ile	Arg	Val 265	Thr	Cys	Ser	Lys	Lys 270	Ile	Ser
	Leu	Pro	Trp 275													
40	(2) INFO	SEQ	JENCI LEI TYI	FOR S E CHANGTH PE: 8 RANDI	ARAC : 284 amin	reris 4 am: 5 ac:	STIC: ino a id	S: acid:	5							

 $H^{\bullet}(\mathbb{R}^{n}) = \mathbb{R}^{n} \times \mathbb{R}^{n} \times \mathbb{R}^{n} \times \mathbb{R}^{n} \times \mathbb{R}^{n} \times \mathbb{R}^{n} \times \mathbb{R}^{n}$

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	Asn	Leu	Ile	Ile 20	Ile	Ile	Leu	Ile	Leu 25	Leu	Asp	Ser	His	Leu 30	His	Thr
	Pro	Met	Tyr 35	Leu	Phe	Leu	Ser	Asn 40	Leu	Ser	Phe	Ala	Asp 45	Leu	Cys	Phe
5	Ser	Ser 50	Leu	Lys	Leu	Leu	Gln 55	Asn	Met	Gln	Ser	Gln 60	Val	Pro	Ser	Ile
	Pro 65	Tyr	Ala	Gly	Cys	Leu 70	Ala	Gln	Ile	Tyr	Phe 75	Phe	Leu	Phe	Phe	Gly 80
10	Asp	Leu	Gly	Asn	Phe 85	Leu	Leu	Val	Ala	Me t 90	Ala	Tyr	qaA	Arg	Tyr 95	Val
	Ala	Ile	Сув	Phe 100	Pro	Leu	His	Tyr	Met 105	Ser	Ile	Met	Ser	Pro 110	Lys	Ile
	Glx	Val	Ser 115	Leu	Val	Val	Leu	Ser 120	Trp	Val	Leu	Thr	Thr 125	Phe	His	Ala
15	Met	Leu 130	His	Thr	Leu	Ile	Met 135	Ala	Arg	Leu	Ser	Phe 140	Сув	Gl.	Asp	Ser
	Val 145	Ile	Pro	His	Tyr	Phe 150	Cys	Asp	Met	Ser	Thr 155	Leu	Leu	Lys	Val	Ala 160
20	Cys	Ser	Asp	Thr	His 165	Asp	Asn	Glu	Leu	Ala 170	Ile	Phe	Ile	Leu	Gly 175	Gly
	Pro	Ile	Val	Val 180	Leu	Pro	Phe	Leu	Leu 185	Ile	Ile	Val	Ser	Tyr 190	Ala	Arg
	Ile	Val	Ser 195	Ser	Ile	Phe	Lys	Val 200	Pro	Ser	Ser	Gln	Ser 205	Ile	His	Lys
25	Ala	Phe 210	Ser	Thr	Сув	Gly	Ser 215	His	Leu	Ser	Val	Val 220	Ser	Leu	Phe	Tyr
	Gly 225	Thr	Val	Ile	Gly	Leu 230	Tyr	Leu	Cys	Pro	Ser 235	Ala	Asn	Asn	Ser	Glu 240
30	Val	Lys	Glu	Thr	Val 245	Met	Ser	Ile	Tyr	Thr 250	Met	Val	Pro	Met	Leu 255	Asn
	Pro	Phe	Ile	Tyr 260	Ser	Leu	Arg	Asn	Arg 265	Asp	Ile	Lys	qaA	Ala 270	Leu	Glu
	Lys	Ile	Met 275	Сув	Lys	Lys	Gln	Ile 280	Pro	Ser	Phe	Leu				
35 40	(2) INFOR (i)	SEQU (A) (B) (C)		CHA IGTH: PE: & RANDE	ARACT 277 mino EDNES	TERIS ami aci SS: s	STICS ino a id singl	S: acids	3							
	(ii)	MOLE	CULE	TY	PE: p	epti	de									
	(xi) Leu 1	SEQU Phe									Leu	Thr	Ile	Ile	Leu 15	Gly
45	Asn	Leu	Leu	Ile 20	Ile	Val	Leu	Val	Arg 25	Leu	Asp	Ser	His	Leu 30	His	Met

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	Tyr	Leu	Phe 35	Leu	Ser	Asn	Leu	Ser 40	Phe	Ser	Asp	Leu	Cys 45	Phe	Ser	Ser
	Val	Thr 50	Trp	Lys	Leu	Leu	Gln 55	Asn	Met	Gln	Ser	Gln 60	Val	Pro	Ser	Ile
5	Ser 65	Tyr	Thr	Gly	Cys	Leu 70	Thr	Gln	Leu	Tyr	Phe 75	Phe	Met	Val	Phe	Gly 80
	Asp	Trp	Ser	Phe	Leu 85	Leu	Val	Val	Met	Ala 90	Tyr	Asp	Arg	Tyr	Val 95	Ala
10	Ile	Cys	Phe	Pro 100	Leu	Arg	Tyr	Thr	Thr 105	Ile	Met	Ser	Thr	Lys 110	Phe	Cys
	Ala	Ser	Leu 115	Val	Leu	Leu	Leu	Trp 120	Met	Leu	Thr	Met	Arg 125	His	Ala	Leu
	Leu	His 130	Thr	Leu	Leu	Ile	Ala 135	Arg	Leu	Ser	Phe	Cys 140	Glu	Asp	Ser	Val
15	Ile 145	Leu	His	Phe	Phe	Cys 150	Asp	Ile	Ser	Ala	Leu 155	Leu	Lys	ren	Ser	Cys 160
	Ser	Asp	Ile	Tyr	Val 165	Asn	Glu	Leu	Met	Ile 170	Tyr	Ile	Leu	Gly	Gly 175	Leu
20	Ile	Ile	Ile	Ile 180	Pro	Phe	Leu	Leu	Ile 185	Val	Met	Ser	Tyr	Val 190	Arg	Ile
	Phe	Phe	Ser 195	Ile	Leu	Lys	Phe	Pro 200	Ser	Ile	Gln	Asp	Ile 205	Тут	Lys	Val
	Phe	Ser 210	Thr	Cys	Gly	Ser	His 215	Leu	Ser	Val	Val	Thr 220	Leu	Phe	Tyr	Gly
25	Thr 225	Ile	Phe	Gly	Ile	Tyr 230	Leu	Cys	Pro	Ser	Gly 235	Asn	Asn	Ser	Thr	Val 240
	Lys	Glu	Ile	Leu	Thr 245	Val	Val	Thr	Pro	Met 250	Ile	Asn	Pro	Phe	Ile 255	Tyr
30	Ser	Leu	Arg	Asn 260	Arg	qaA	Trp	Arg	Ala 265	Leu	Ile	Arg	Val	Ile 270	Cys	Thr
	Lys	Lys	Ile 275	Ser	Leu											

(2) INFORMATION FOR SEQ ID NO:69:

- (i) SEQUENCE CHAPACTERISTICS:
 - (A) LENGTH: 274 amino acids (B) TYPE: amino acid

 - (C) STRANDEDNESS: single (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:69: Val Phe Tyr Ala Leu Phe Leu Ser Met Tyr Leu Thr Ile Val Leu Gly 40
- Fro Met Tyr Leu Phe Leu Ser Asn Leu Se: Fne Se: Asp Leu Cys Fne 35 40 45 45

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		Ser	Ser 50	Leu	Lys	Leu	Leu	Gln 55	Asn	Met	Gln	Ser	Gln 60	Val	Pro	Ser	Ile
		Pro 65	Phe	Ala	Gly	Cys	Leu 70	Thr	Gln	Leu	Tyr	Phe 75	Tyr	Leu	Tyr	Phe	Ala 80
5		Asp	Leu	Glu	Ser	Phe 85	Leu	Leu	Val	Ala	Met 90	Ala	Tyr	Asp	Arg	Tyr 95	Val
		Ala	Ile	Cys	Phe 100	Pro	Leu	His	Tyr	Met 105	Ser	Ile	Met	Ser	Pro 110	Lys	Leu
10		Cys	Val	Ser 115	Leu	Trp	Leu	Ser	Trp 120	Val	Leu	Thr	Thr	Phe 125	His	Ala	Met
		Leu	His 130	Thr	Leu	Ile	Met	Ala 135	Arg	Leu	Ser	Phe	Cys 140	Ala	Asp	Leu	Pro
		His 145	Phe	Phe	Cys	Asp	Ile 150	Ser	Pro	Leu	Leu	Lys 155	Leu	Ser	Cys	Ser	Asp 160
15		Thr	His	Val	Asn	Glu 165	Leu	Val	Ile	Phe	Leu 170	Gly	Leu	Val	Ile	Val 175	Ile
		Pro	Phe	Val	Leu 180	Ile	Ile	Val	Ser	Tyr 185	Ala	Arg	Val	Val	Ala 190	Ser	Ile
20		Leu	Lys	Val 195	Pro	Ser	Val	Arg	Gly 200	Ile	His	Lys	Ile	Phe 205	Ser	Thr	Cys
		Gly	Ser 210	His	Leu	Ser	Val	Val 215	Ser	Leu	Phe	Tyr	Gly 220	Thr	Ile	Ile	Gly
		Leu 225	Tyr	Leu	Cys	Pro	Ser 230	Ala	Asn	naA	Ser	Thr 235	Val	Lys	Glu	Thr	Leu 240
25		Thr	Val	Val	Thr	Pro 245	Leu	Pro	Phe	Ile	Tyr 250	Ser	Leu	Arg	Asn	Arg 255	Asp
		Met	Lys	Glu	Ala 260	Leu	Ile	Arg	Val	Leu 265	Cys	Lys	Lys	Lys	Ile 270	Thr	Phe
30		Cys	Leu														
35	(2)		SEQUA)	JENCE LEI TYI	CHA IGTH: PE: 8	ARĀC: 345 mino	reris am:	STICS ino a	S: acids	5							
		(ii)		TOI													
40		(xi) Leu 1	_	JENCI Ile					-			Leu	Gly	Thr	Phe	Thr 15	Val
		Leu	Glu	Asn	Leu 20	Leu	Val	Leu	Cys	Val 25	Ile	Leu	His	Ser	Arg 30	Ser	Leu
		Arg	Cys	Arg 35	Pro	Ser	Tyr	His	Phe 40	Ile	Gly	Ser	Leu	Ala 45	Val	Ala	Asp
4 5		Leu	Leu 50	Gly	Ser	Val	Ile	Phe 55	Val	Tyr	Ser	Phe	Val 60	Asp	Phe	His	Val
		Phe 65	His	Arg	Lys	Asp	Ser 70	Pro	Asn	Val	Phe	Leu 75	Phe	Lys	Leu	Gly	Gly 80

 $(E^{\bullet}A)(1) = (1 + A) + (2 + A) + (3 + A) + (3 + A)$

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		Val	Thr	Ala	Ser	Phe 85	Thr	Ala	Ser	Val	Gly 90	Ser	Leu	Phe	Leu	Thr 95	Ala
		Ile	Asp	Arg	Tyr 100	Ile	Ser	Ile	His	Pro 105	Pro	Ile	Ala	Tyr	Lys 110	Arg	Ile
5		Val	Arg	Arg 115	Pro	Lys	Ala	Val	Val 120	Ala	Phe	Cys	Leu	Met 125	Thr	Ile	Ala
		Ile	Val 130	Ile	Ala	Val	Leu	Pro 135	Leu	Leu	Gly	Trp	Asn 140	Cys	Lys	Lys	Leu
10		Gln 145	Ser	Val	Cys	Cys	Asp 150	Ile	Phe	Pro	Leu	Ile 155	Asp	Gly	Thr	Tyr	Leu 160
		Met	Phe	Trp	Ile	Gly 165	Val	Thr	Ser	Val	Leu 170	Leu	Leu	Phe	Ile	Val 175	Tyr
		Ala	Tyr	Met	Tyr 180	Ile	Leu	Trp	Lys	Ala 185	His	Ser	His	Ala	Val 190	Arg	Ala
15		Gln	Arg	Gly 195	Thr	Gln	Lys	Ser	Ile 200	Ile	Ile	His	Thr	Ser 205	Glu	Asp	Gly
		Lys	Val 210	Gln	Val	Thr	Arg	Pro 215	Asp	Gln	Ala	Arg	Met 220	Asp	Ile	Arg	Leu
20		Ala 225	Lys	Thr	Leu	Val	Leu 230	Ile	Leu	Val	Val	Leu 235	Ile	Ile	Cys	Trp	Gly 240
		Pro	Leu	Leu	Ala	Ile 245	Met	Val	Tyr	Asp	Val 250	Phe	Gly	Leu	Leu	Ile 255	Lys
		Thr	Val	Phe	Ala 260	Phe	Cys	Ser	Leu	Leu 265	Ile	Asn	Ser	Thr	Val 270	Asn	Pro
25		Ile	Ile	Tyr 275	Ala	Leu	Arg	Ser	Lys 280	Asp	Leu	Arg	His	Ala 285	Phe	Arg	Ser
		Trp	Pro 290	Ser	Cys	Glu	Gly	Thr 295	Ala	Gln	Pro	Leu	Asp 300	Asn	Ser	Met	Gly
30		Asp 305	Ser	Asp	Cys	Leu	His 310	Lys	His	Ala	Asn	Asn 315	Thr	Ala	Se _r	Met	His 320
		Arg	Ala	Ala	Glu	Ser 325	Cys	Ile	Lys	Ser	Thr 330	Val	Lys	Leu	Ala	Leu 335	Val
		Ser	Thr	Asp	Thr 340		Ala	Glu	Ala	Le u 3 4 5							
35	(2)		SEQ (A (B	ION UENC) LE) TY) ST	E CH NGTH PE:	ARAC : 34 amin	TERI 9 am o ac	STIC ino id	S: acid	s							
40		(ii)	MOL) TO ECUL	POLO E TY	GY: PE:	line pept	ar ide			4 .						
									-								

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	Ile	Ser	Ala 35	Thr	Ser	Leu	Phe	Ile 40	Val	Asn	Leu	Ala	Val 45	Ala	qaA	Ile
	Ile	Glu 50	Thr	Leu	Leu	Asn	Thr 55	Pro	Phe	Thr	Leu	Val 60	Arg	Phe	Val	Asn
5	Ser 65	Thr	Trp	Tyr	Phe	Gly 70	Lys	Gly	Met	Leu	His 75	Val	Ser	Arg	Phe	Ala 80
	Gln	Tyr	Cys	Ser	Leu 85	His	Val	Ser	Ala	Leu 90	Ile	Leu	Thr	Ala	Ile 95	Ala
10	Val	Asp	Arg	His 100	Gln	Val	Ile	Met	Pro 105	Leu	Lys	Pro	Arg	Ile 110	Ser	Ile
	Thr	Lys	Gly 115	Val	Ile	Tyr	Ile	Ala 120	Val	Ile	Trp	Val	Met 125	Thr	Phe	Phe
	Ser	Leu 130	Pro	His	Ala	Ile	Сув 135	Gln	Lys	Leu	Phe	Thr 140	Phe	Lys	Tyr	Ser
15	Glu 145	Asp	Ile	Val	Arg	Ser 150	Leu	Cys	Leu	Asp	Pro 155	Phe	Pro	Glu	Pro	Ala 160
	qaA	Leu	Phe	Trp	Lys 165	Tyr	Leu	Asp	Ile	Ala 170	Thr	Phe	Ile	Leu	Leu 175	Tyr
20	Leu	Leu	Pro	Leu 180	Phe	Ile	Ile	Ser	Val 185	Ala	Tyr	Ala	Arg	Val 190	Ala	Lys
	Lys	Leu	Trp 195	Leu	Сув	Asn	Thr	Ile 200	Gly	Asp	Val	Thr	Thr 205	Glu	Gln	Tyr
	Leu	Ala 210	Leu	Arg	Arg	Lys	Lys 215	Lys	Thr	Thr	Val	Lys 220	Met	Leu	Val	Leu
25	Val 225	Val	Val	Leu	Phe	Ala 230	Leu	Cys	Trp	Phe	Pro 235	Leu	Asn	Cys	Tyr	Val 240
	Leu	Leu	Leu	Ser	Ser 245	Lys	Ala	Ile	His	Thr 250	Asn	Asn	Ala	Leu	Tyr 255	Phe
30	Ala	Phe	His	Trp 260	Phe	Ala	Met	Ser	Ser 265	Thr	Cys	Tyr	Asn	Pro 270	Phe	Ile
	Tyr	Cys	Trp 275	Leu	Asn	Glu	Asn	Phe 280	Arg	Val	Glu	Leu	Lys 285	Ala	Leu	Leu
	Ser	Met 290	Gln	Pro	Pro	Pro	Lys 295	Pro	Glu	Asp	Arg	Leu 300	Pro	Ser	Pro	Val
35	Pro 305	Ser	Phe	Arg	Val	Ala 310	Trp	Thr	Glu	Lys	Ser 315	His	Gly	Arg	Arg	Ala 320
	Pro	Leu	Pro	Asn	His 325	His	Leu	Pro	Ser	Ser 330	Gln	Ile	Gln	Ser	Gly 335	Lys
40	Thr	Asp	Leu	Ser 340	Ser	Val	Glu	Pro	Val 345	Val	Ala	Met	Ser			

(2) INFORMATION FOR SEQ ID NO:72: (i) SEQUENCE CHARACTERISTICS:

- - (A) LENGTH: 301 amino acids
 - (B) TYPE: amino acid
- (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: peptide

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	(xi)	SEQU	JENCE	E DES	SCRIE	PTION	N: SE	EQ II	NO.	:72:						
	Ile 1	Phe	Thr	Ile	Ala 5	Leu	Ala	Tyr	Gly	Ala 10	Val	Ile	Ile	Leu	Gly 15	Val
5	Ser	Gly	Asn	Leu 20	Ala	Leu	Ile	Ile	Ile 25	Ile	Leu	Lys	Gln	Lys 30	Glu	Leu
	Ile	Leu	Ile 35	Val	Asn	Leu	Ser	Phe 40	Ser	Asp	Leu	Leu	Val 45	Ala	Val	Trp
	Leu	Pro 50	Phe	Thr	Phe	Val	Tyr 55	Thr	Leu	Ile	Cys	His 60	Trp	Val	Phe	Gly
10	Glu 65	Cys	Cys	Lys	Leu	Asn 70	Pro	Phe	Val	Gln	Cys 75	Val	Ser	Ile	Thr	Val 80
	Ser	Ile	Phe	Ser	Leu 85	Val	Leu	Ile	Ala	Val 90	Glu	Arg	His	G1	Leu 95	Ile
15	Ile	Asn	Pro	Arg 100	Gly	Trp	Arg	Pro	Asn 105	Asn	Arg	His	Ala	Tyr 110	Ile	Gly
	Ile	Thr	Val 115	Ile	Trp	Val	Ile	Ala 120	Val	Ala	Ser	Ser	Leu 125	Pro	Phe	Val
	Ile	Tyr 130	Gln	Ile	Leu	Thr	Asp 135	Glu	Pro	Phe	Gln	Asn 140	Val	Ser	Leu	Ala
20	Ala 145	Phe	Lys	Asp	Lys	Tyr 150	Val	Cys	Phe	Asp	Lys 155	Phe	Pro	Ser	Asp	Ser 160
	His	Arg	Leu	Ser	Tyr 165	Thr	Thr	Leu	Leu	Leu 170	Val	Leu	Gln	Tyr	Phe 175	Gly
25	Pro	Leu	Cys	Phe 180	Ile	Phe	Ile	Сув	Tyr 185	Phe	Lys	Ile	Tyr	Ile 190	Arg	Leu
	Lys	Arg	Arg 195	Asn	Asn	Met	Met	Lys 200	Ile	Arg	Asp	Ser	Lys 205	Tyr	Arg	Ser
	Ser	Glu 210	Thr	Lys	Arg	Ile	Asn 215	Val	Met	Leu	Leu	Ser 220	Ile	Val	Val	Ala
30	Phe 225	Ala	Val	Cys	Trp	Leu 230	Pro	Leu	Thr	Ile	Phe 235	Asn	Ile	۷a.	Phe	Asp 240
	Trp	Asn	His	Gln	Ile 2 4 5	Ile	Ala	Thr	Cys	Asn 250	His	Asn	Leu	Leu	Phe 255	Leu
35	Leu	Cys	His	Leu 260	Thr	Leu	Ser	Thr	Cys 265	Val	Asn	Pro	Ile	Phe 270	Tyr	Gly
	Phe	Leu	Asn 275	Lys	Asn	Phe	Gln	Arg 280	Asp	Leu	Gln	Phe	Phe 285	Phe	Asn	Phe
	Cys	Asp 290	Phe	Arg	Ser	Arg	Asp 295	_	Arg	Thr	Thr	Arg 300	Leu			
4.0	TOTAL TRIPO	ייי א א כו	てつわ :	tino	೧೮೧	TTI N	A - 73									

40 TO INFORMATION FOR SEQ ID NOTE:

*: 1

 $A(X_{k+1}) = \{1, \dots, X_{k+1}, \dots, A(X_{k+1}) \in A(X_{k+1}) \mid A(X_{k+1}) \in A(X_{k+1}) \}$

TRANDEDNESS TIPE + (D. TOPOLOGY: linear 11. MOLECULE TYPE: peptide

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	(xi) Leu l	SEQ Thr	UENC Ser	E DE Val	SCRI Val 5	PTIO: Phe	N: S Ile	EQ I Leu	D NO Ile	:73: Cys 10	Cys	Phe	Ile	Ile	Leu 15	Glu
5	Asn	Ile	Phe	Val 20	Leu	Leu	Thr	Ile	Trp 25	Lys	Thr	Lys	Lys	Phe 30	His	Arg
	Pro	Met	Tyr 35	Tyr	Phe	Ile	Gly	Asn 40	Ile	Ala	Leu	Ser	Asp 45	Leu	Ile	Ala
	Gly	Val 50	Ala	Tyr	Thr	Ala	Asn 55	Leu	Leu	Leu	Ser	Gly 60	Ala	Thr	Thr	Tyr
10	Lys 65	Leu	Thr	Pro	Ala	Gln 70	Trp	Phe	Leu	Arg	Glu 75	Gly	Ser	Met	Phe	Val 80
	Ala	Leu	Ser	Leu	Ser 85	Val	Phe	Ser	Leu	Leu 90	Ala	Ile	Ala	Ile	Glu 95	Arg
15	Tyr	Ile	Thr	Met 100	Leu	Lys	Met	Leu	His 105	Asn	Gly	Ser	Asn	Asn 110	Phe	Arg
	Leu	Phe	Leu 115	Leu	Ile	Ser	Ala	Cys 120	Trp	Val	Ile	Ser	Leu 125	Ile	Leu	Gly
	Gly	Leu 130	Pro	Ile	Met	Gly	Trp 135	Asn	Cys	Ile	Ser	Ala 140	Leu	Ser	Ser	Cys
20	Ser 145	Thr	Val	Leu	Pro	Leu 150	Tyr	His	Lys	His	Tyr 155	Ile	Leu	Phe	Cys	Thr 160
	Leu	Ile	Val	Phe	Thr 165	Leu	Leu	Leu	Leu	Ser 170	Ile	Val	Ile	Leu	Tyr 175	Cys
25			Tyr	180					185					190		
			Ile 195					200					205			
2.0		210	Val				215					220				
30	225		Ile			230					235					240
			Leu		245					250					255	
35			Thr	260					265					270		
	Arg		2/5					280					285			
		290	Lys				295					300				
40	305		Ser			310					315				Asp	Asn 320
	Pro	Glu	Thr	Ile	Met 325	Ser	Ser	Gly	Asn	Val 330	Asn	Ser	Ser	Ser		

(2) INFORMATION FOR SEQ ID NO:74:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 236 amino acids

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		(ii)	(C) (D)	TYI STI TOI CULI	OLOC	EDNES	SS: s linea	sing] ar	.e								
5		(xi) Ile 1	SEQU Thr									Ala	Val	Val	Gly	Asn 15	Ile
		Leu	Leu	Val	Ile 20	Trp	Val	Val	Lys	Leu 25	Asn	Arg	Thr	Leu	Arg 30	Thr	Thr
10		Thr	Phe	Tyr 35	Phe	Ile	Val	Ser	Ile 40	Ala	Leu	Ala	Asp	Ile 45	Ala	Val	Leu
		Val	Ile 50	Pro	Leu	Ala	Ile	Ala 55	Ser	Ala	Trp	Arg	Ser 60	Arg	Cys	Thr	Ser
15		Aan 65	Cys	Leu	Phe	Met	Ser 70	Cys	Val	Leu	Leu	Val 75	Phe	Thr	His	Ala	Ser 80
		Ile	Met	Ser	Leu	Leu 85	Ala	Ile	Ala	Val	Asp 90	Arg	Tyr	Leu	Arg	Val 95	Lys
		Leu	Thr	Val	Arg 100	Tyr	Arg	Thr	Val	Thr 105	Thr	Gln	Arg	Arg	Ile 110	Trp	Leu
20		Phe	Leu	Gly 115	Leu	Cys	Trp	Leu	Val 120	Ser	Phe	Leu	Val	Gly 125	Leu	Thr	Pro
		Trp	Gly 130	Trp	Asn	Arg	Lys	Val 135	Thr	Leu	Glu	Leu	Ser 140	Gln	Asn	Ser	Ser
25		Thr 145	Leu	Arg	Glu	Phe	Lys 150	Thr	Pro	Lys	Ser	Leu 155	Phe	Leu	Val	Leu	Phe 160
		Leu	Phe	Ala	Leu	Cys 165	Trp	Leu	Pro	Leu	Ser 170	Ile	Ile	Asn	Phe	Val 175	Ser
		Tyr	Phe	Asn	Val 180	Lys	Ile	Pro	Glu	Thr 185	Leu	Leu	Gly	Ile	Leu 190	Leu	Ser
30		His	Ala	Asn 195	Ser	Leu	Pro	Ile	Val 200	Tyr	Ala	Cys	Lys	Lys 205	Lys	P'ne	Lys
		Glu	Thr 210	Tyr	Phe	Val	Ile	Leu 215	Arg	Ala	Cys	Arg	Leu 220	Cys	Gln	Thr	Ser
35		Asp 225	Ser	Leu	Asp	Ser	Asn 230	Leu	Glu	Gln	Thr	Thr 235	Glu				
	(2)	INFO	SEQI (A)	UENC:	E CHI NGTH	ARĀC' : 32:	reri: 2 am:	STIC:	S :	s							
40			(C) TY:) ST:) TO:	RAND	ED NE .	SS:	sing	le								

Thr Ala Thr Asn Ile Tyr Ile Leu Asn Ile Ala Ile Ala Asp Glu Leu

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(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75

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				35					40					45			
		Leu	Val 50	Pro	Phe	Leu	Val	Thr 55	Ser	Thr	Leu	Leu	Arg 60	His	Trp	Pro	Phe
5		Gly 65	Ala	Leu	Leu	Cys	Arg 70	Leu	Val	Leu	Ser	Val 75	Asp	Ala	Val	Asn	Me t 80
		Phe	Thr	Ser	Ile	Tyr 85	Сув	Leu	Thr	Val	Leu 90	Ser	Val	Asp	Arg	Tyr 95	Val
		Ala	Val	Val	His 100	Pro	Ile	Lys	Ala	Ala 105	Arg	Tyr	Arg	Arg	Pro 110	Thr	Val
10		Ala	Lys	Val 115	Val	Asn	Leu	Gly	Val 120	Trp	Val	Leu	Ser	Leu 125	Leu	Val	Ile
		Leu	Pro 130	Ile	Trp	Phe	Ser	Arg 135	Thr	Ala	Ala	Asn	Ser 140	Asp	Gly	Thr	Val
15		Ala 145	Сув	Asn	Met	Ile	Trp 150	Glu	Pro	Ala	Gln	Phe 155	Trp	Leu	Vai	Gly	Phe 160
		Val	Leu	Tyr	Thr	Phe 165	Leu	Met	Phe	Leu	Leu 170	Pro	Val	Gly	Ala	Ile 175	Cys
		Leu	Cys	Tyr	Val 180	Leu	Ile	Ile	Ala	Lys 185	Met	Arg	Met	Val	Ala 190	Leu	Lys
20		Ala	Gly	Trp 195	Gln	Gln	Arg	Lys	Arg 200	Ser	Glu	Arg	Lys	Ile 205	Thr	Leu	Val
		Met	Met 210	Val	Val	Met	Val	Phe 215	Val	Ile	Cys	Trp	Phe 220	Tyr	Val	Val	Gln
25		Leu 2 2 5	Val	Asn	Val	Phe	Ala 230	Glu	Gln	Asp	Asp	Ala 235	Thr	Val	Ser	Gln	Leu 240
		Ser	Val	Ile	Leu	Gly 245	Tyr	Ala	Asn	Ser	Сув 250	Ala	Asn	Pro	Ile	Leu 255	Tyr
		Gly	Phe	Leu	Ser 260	qaA	Asn	Phe	Lys	Arg 265	Ser	Phe	Gln	Arg	Ile 270		ayD
30		Leu	Ser	Leu 275	Asn	Ala	Ala	Glu	Glu 280	Pro	Val	qaA	Tyr	Tyr 285	Ala	Thr	Ala
		Leu	Lys 290	Ser	Arg	Ala	Tyr	Ser 295	Val	Glu	Asp	Phe	Gln 300	Pro	Glu	Asn	Leu
35		Glu 305	Ser	Gly	Gly	Val	Phe 310	Arg	Asn	Cys	Thr	Cys 315	Ala	Ser	Arg	Ile	Ser 320
		Thr	Leu														
40	(2)		SEQU (A) (B) (C) (D)	ENCE LEN TYP STR TOP	CHAIGTH: PE: 8 PANDE POLOG	SEQ I ARACT 298 minc DNES Y: 1	ERIS ami aci S: s inea	TICS no a d ingl	: cids	:							
45		(xi) Val	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID Leu	NO: Leu	76: Cys 10	Leu	Cys	Gly	Le∙u	Val 15	Gly

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		Asn	Gly	Leu	Val 20	Leu	Trp	Phe	Phe	Gly 25	Phe	Ser	Ile	Lys	Arg 30	Thr	Pro
		Phe	Ser	Ile 35	Tyr	Ile	Tyr	Phe	Leu 40	His	Ile	Ala	Ser	Ala 45	Asp	Gly	Ile
5		Tyr	Leu 50	Phe	Ser	Lys	Ala	Val 55	Ile	Ala	Leu	Leu	Asn 60	Met	Gly	Thr	Phe
		Leu 65	Gly	Ser	Phe	Pro	Asp 70	Tyr	Val	Arg	Arg	Val 75	Ser	Arg	Ile	Val	Gly 80
10		Leu	Thr	Phe	Phe	Ala 85	Gly	Val	Ser	Leu	Leu 90	Pro	Ala	Ile	Ser	Ile 95	Glu
		Arg	Cys	Val	Ser 100	Val	Ile	Phe	Pro	Me t 105	Trp	Tyr	Trp	Arg	Arg 110	Arg	Pro
		Lys	Arg	Leu 115	Ser	Ala	Gly	Val	Cys 120	Ala	Leu	Leu	Trp	Leu 125	Leu	Ser	Phe
15		Leu	Val 130	Thr	Ser	Ile	His	Asn 135	Tyr	Phe	Cys	Leu	Leu 140	Gly	His	Glu	Ala
		Ser 145	Gly	Thr	Ala	Cys	Leu 150	Asn	Met	Asp	Ile	Ser 155	Leu	Leu	Gly	Ile	Leu 160
20		Leu	Phe	Phe	Leu	Phe 165	Cys	Pro	Ile	Met	Val 170	Leu	Pro	Cys	Ile	Ala 175	Leu
		Leu	His	Val	Glu 180	Сув	Arg	Ala	Arg	Arg 185	Arg	Gln	Arg	Ser	Ala 190	Lys	Leu
		Asn	His	Val 195	Val	Leu	Ala	Ile	Val 200	Ser	Val	Phe	Leu	Val 205	Ser	Ser	Ile
25		Tyr	Leu 210	Gly	Ile	Asp	Trp	Phe 215	Leu	Phe	Trp	Val	Phe 220	Gln	Ile	Pro	Ala
		Pro 225	Phe	Pro	Glu	Tyr	Val 230	Arg	Asp	Leu	Cys	Ile 235	Cys	Ile	Asn	Ser	Ser 240
30		Ala	Lys	Pro	Ile	Val 245	Tyr	Phe	Ile	Ala	Gly 250	Arg	Asp	Lys	Ser	Gln 255	Arg
		Leu	Trp	Glu	Pro 260	Leu	Arg	Val	Val	Phe 265	Gln	Arg	Ala	Leu	Arg 270	Asp	Gly
		Ala	Glu	Pro 275	Gly	Asp	Ala	Ala	Ser 280	Ser	Thr	Pro	Asn	Thr 285	۷a۱	Thr	Met
35		Glu	Met 290	Gln	Cys	Pro	Ser	Gly 295	Asn	Ala	Ser						
40	(2)		SEQI (A	ION : UENC:) LE:) TY:	E CHA	ARAC' : 29	TERI:	STIC	S :	s							
			(C) ST) TO:	RANDI	EDNE.	SS:	sing	le								

Ala Ile Val Leu Ile Thr Gln Leu Leu Thr Asn Arg Val Leu Gly Tyr

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				20					25					30		
	Ser	Thr	Pro 35	Thr	Ile	Tyr	Met	Arg 40	Asn	Leu	Tyr	Ser	Thr 45	Asn	Phe	Leu
5	Thr	Leu 50	Thr	Val	Leu	Pro	Phe 55	Ile	Val	Leu	Ser	Asn 60	Gln	Trp	Leu	Leu
	Pro 65	Ala	Cys	Tyr	Val	Ala 70	Ser	Cys	Lys	Phe	Leu 75	Ser	Val	Ile	Tyr	Tyr 80
	Ser	Ser	Cys	Thr	Val 85	Gly	Phe	Ala	Thr	Val 90	Ala	Leu	Ile	Ala	Ala 95	Asp
10	Arg	Tyr	Arg	Val 100	Leu	His	Lys	Arg	Thr 105	Tyr	Ala	Arg	Gln	Ser 110	Tyr	Arg
	Ser	Leu	Leu 115	Leu	Thr	Trp	Leu	Ala 120	Gly	Leu	Ile	Phe	Ser 125	Val	Pro	Ala
15	Ala	Val 130	Tyr	Thr	Thr	Val	Val 135	Met	His	His	Asp	Ala 140	Asn	Asp	Thr	Asn
	Asn 145	Thr	Asn	Gly	His	Ala 150	Thr	Cys	Val	Leu	Tyr 155	Phe	Val	Ala	Glu	Glu 160
	Val	His	Thr	Val	Leu 165	Leu	Ser	Trp	Lys	Val 170	Leu	Leu	Thr	Met	Val 175	Trp
20	Gly	Ala	Ala	Pro 180	Val	Ile	Leu	Phe	Tyr 185	Ala	Phe	Phe	Tyr	Se~ 190	Thr	Val
	Gln	Arg	Thr 195	Ser	Gln	Lys	Gln	Arg 200	Ser	Arg	Thr	Leu	Thr 205	Phe	Val	Ser
25	Val	Leu 210	Leu	Ile	Ser	Phe	Val 215	Ala	Leu	Gln	Thr	Pro 220	Tyr	Val	Ser	Leu
	Met 225	Ile	Phe	Asn	Ser	Tyr 230	Ala	Thr	Thr	Ala	Trp 235	Pro	Met	Cys	Glu	His 240
	Leu	Thr	Leu	Arg	Arg 245	Thr	Ile	Gly	Thr	Leu 250	Ala	Arg	Val	Val	Pro 255	His
30	Leu	His	Cys	Leu 260	Ile	Asn	Pro	Ile	Leu 265	Tyr	Ala	Leu	Leu	Cys 270	His	Asp
	Phe	Leu	Gln 275	Arg	Met	Arg	Gln	Cys 280	Phe	Arg	Gly	Gln	Leu 285	Ile	Asp	Arg
35	Ala	Phe 290	Leu	Arg	Ser	Gln	Gln 295	Asn	Gln	Arg	Ala					
	(2) INFO	SEQ	ION I UENCI) LEI	E CH	ARĀC'	reri:	STIC	S:	s							
40	(ii)	(B (C (D) TYI) STI) TOI	PE: 6 RANDI POLO	amino EDNES GY:	o ac: SS: : linea	id sing: ar									
45			UENCI Val								Phe	Leu	Leu	Val	Ile 15	Thr
	Thr	Ile	Leu	Tyr 20	Tyr	Arg	Arg	Lys	Lys 25	Lys	Ser	Pro	Ser	Asກ 30	Thr	Tyr

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		Ile	Cys	Asn 35	Leu	Ala	Val	Ala	Asp 40	Leu	Leu	Ile	Val	Val 45	Gly	Leu	Pro
		Phe	Phe 50	Leu	Glu	Tyr	Ala	Lys 55	His	His	Pro	Lys	Leu 60	Ser	Arg	Glu	Val
5		Val 65	Cys	Ser	Gly	Leu	Asn 70	Ala	Сув	Phe	Tyr	Ile 75	Cys	Leu	Phe	Ala	Gly 80
		Val	Cys	Phe	Leu	Ile 85	Asn	Leu	Ser	Met	Asp 90	Arg	Tyr	Cys	Val	Ile 95	Val
10		Trp	Gly	Val	Glu 100	Leu	Asn	Arg	Val	Arg 105	Asn	naA	Lys	Arg	Ala 110	Thr	Cys
		Trp	Val	Val 115	Ile	Phe	Trp	Ile	Ile 120	Ala	Val	Leu	Met	Gly 125	Met	Pro	His
		Tyr	Ile 130	Met	Tyr	Ser	His	Thr 135	Asn	Asn	Glu	Cys	Val 140	Gly	Trp	Phe	Ala
15		Asn 145	Glu	Thr	Ser	Cys	Trp 150	Phe	Pro	Val	Phe	Leu 155	Asn	Thr	Ly.	Val	Asn 160
		Ile	Cys	Gly	Tyr	Leu 165	Ala	Pro	Ile	Ala	Leu 170	Met	Ala	Tyr	Tyr	Asn 175	Arg
20		Met	Val	Arg	Phe 180	Ile	Ile	Asn	Tyr	Val 185	Gly	Lys	Trp	Phe	Met 190	Gln	Thr
		Leu	His	Val 195	Leu	Leu	Val	Val	Val 200	Val	Ser	Phe	Ala	Ser 205	Phe	Trp	Phe
		Pro	Phe 210	Asn	Leu	Ala	Leu	Phe 215	Leu	Glu	Ser	Ile	Arg 220	Leu	Ile	Ala	Gly
25		Val 225	Tyr	Asn	Asp	Thr	Leu 230	Gln	Asn	Val	Ile	Ile 235	Phe	Cys	Leu	Tyr	Val 240
		Gly	Gln	Phe	Ile	Ala 245	Tyr	Val	Arg	Ala	Cys 250	Leu	Asn	Pro	Gly	Ile 255	Tyr
30		Ile	Leu	Val	Cys 260	Thr	Trp	Phe	Leu	Arg 265	Val	Phe	Ala	Cys	Cys 270	Cys	Val
		Lys	Gln	Glu 275	Ile	Pro	Tyr	Gln	Asp 280	Ile	Asp	Ile					
35	(2)		SEQ (A (B (C (D	UENC:) LEI) TY:) ST:) TO	E CH NGTH PE: RAND POLO	ARÂC : 29 amin EDNE GY:	TERI 5 am o ac	STIC ino id sing ar	S: acid	s							
40								N: S Tyr				Phe	Leu	Phe	Gly	Ser	Ile

46 45

Phe Val Cys Thr Leu Pro Leu Trp Met Gln Tyr Leu Leu Ast His Asn

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			50					55					60				
		Ser 65	Leu	Ala	Ser	Leu	Ile 70	Pro	Cys	Thr	Leu	Leu 75	Thr	Ala	Cys	Phe	Tyr 80
5		Val	Ala	Ile	Thr	Ala 85	Ser	Leu	Cys	Phe	Ile 90	Thr	Glu	Ile	Ala	Leu 95	Ile
		Asp	Arg	Tyr	Tyr 100	Ala	Ile	Val	Tyr	Met 105	Arg	Tyr	Arg	Pro	Val 110	Lys	Ile
		Gln	Ala	Cys 115	Leu	Phe	Ser	Ile	Phe 120	Trp	Trp	Ile	Phe	Ala 125	Val	Ile	Ile
10		Ala	Ile 130	Pro	His	Phe	Met	Val 135	Val	Ile	Thr	Lys	Lys 140	Asp	Asn	Gln	Cys
		Met 145	Thr	Asp	Tyr	Asp	Tyr 150	Leu	Glu	Val	Ser	Tyr 155	Pro	Ile	Ile	Leu	Asn 160
15		Val	Glu	Leu	Met	Leu 165	Gly	Ala	Phe	Val	Ile 170	Pro	Leu	Ser	Val	Ile 175	Ser
		Tyr	Cys	Tyr	Tyr 180	Arg	Ile	Ser	Arg	Ile 185	Val	Ala	Val	Ser	Gln 190	Ser	Arg
		His	Lys	Gly 195	Arg	Ile	Val	Arg	Val 200	Leu	Ile	Ala	Trp	Leu 205	Val	Phe	Ile
20		Ile	Phe 210	Trp	Leu	Pro	Tyr	His 215	Leu	Thr	Leu	Phe	Val 220	Asp	Thr	Ile	Ile
		Lys 225	Leu	Leu	Lys	Trp	Ile 230	Ser	Ser	Ser	Cys	Glu 235	Phe	Glu	Arg	Ser	Leu 240
25		Lys	Arg	Ala	Leu	Ile 245	Leu	Thr	Glu	Ser	Leu 250	Ala	Phe	Сув	His	Cys 255	Cys
		Leu	Asn	Pro	Leu 260	Leu	Tyr	Val	Phe	Val 265	Ile	Gly	Thr	Lys	Phe 270	Arg	Lys
		Asn	Tyr	Thr 275	Val	Cys	Trp	Pro	Ser 280	Phe	Ala	Ser	Asp	Ser 285	Phe	Pro	Ala
30		Met	Tyr 290	Pro	Gly	Thr	Arg	Ala 295									
35	(2)	INFO	SEQUAL (A)	JENCI LEI TYI STI	S CHI NGTH PE: a RANDI		reris amin ac: SS: 1	STICS no ac id sing	S: cids								
			MOLI	ECULI	E TY	PE: I	pept:	ide	FO T	חוא ר	· a n ·						
40		Asp 1	Asp	Asp	Asp	Asn 5	Ile	Trp	Ser	Ile	Phe 10	Asp	Trp	Ile	Gly	Tyr 15	Leu
		Asn	Ser	Ile	Ser 20	Met	Val	Ile	Tyr	Thr 25	Leu	Phe	Lys	Lys	Lys 30	Lys	
45	(2)	_	SEQI (A (B	JENC:) LE:) TY:	E CHI NGTH PE: 8		reri: amii ac:	STIC: no a id	S: cids								

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(D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:
         Asp Asp Asp Asn Ile Trp Asn Ile Phe Ser Thr Ile Gly Tyr Leu
 5
         Asn Ser Ile Ser Pro Val Ser Val Ile Met His Ile Tyr Gly Lys Lys
         Lys Lys
10
    (2) INFORMATION FOR SEQ ID NO:82:
          (i) SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 29 amino acids
               (B) TYPE: amino acid
               (C) STRANDEDNESS: single
15
               (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:
         Asp Asp Asp Gly Tyr Ser Ile Tyr Asp Thr Leu Val Thr Phe Ala
20
          Ile Asn Pro Val Tyr Ile Thr Val Phe Lys Lys Lys
     (2) INFORMATION FOR SEQ ID NO:83:
          (i) SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 31 amino acids
               (B) TYPE: amino acid
(C) STRANDEDNESS: single
25
               (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:
30
         Asp Asp Asp Asp Asn Ala Trp Ser Ala Phe Asp Trp Ala Leu Tyr Leu
                                               10
         Asn Ser Ile Ser Met Ala Ile Tyr Thr Tyr Ala Lys Lys Lys
                      20
     (2) INFORMATION FOR SEQ ID NO:84:
35
          (i) SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 23 amino acids
               (B) TYPE: amino acid
               (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
40
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:
          Leu Phe Ser Phe Ile Thr Trp Leu Gly Tyr Ala Asn Ser Ser Leu Asn
          Pro Ile Ile Tyr Thr Thr Phe
45
                      20
     (2) INFORMATION FOR SEQ ID NO:85:
          (i) SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 23 amino acids
               (B) TYPE: amino acid
50
               (C) STRANDEDNESS: single
               (D) TOPOLOGY linear
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(2) INFORMATION FOR SEQ ID NO:86:
          (i) SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 22 amino acids
               (B) TYPE: amino acid
 5
               (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:
          Ile Trp Leu Thr Ser Asp Ile Met Ser Thr Ser Ser Ile Leu His Asn
10
          Leu Cys Val Ile Ser Phe
                      20
     (2) INFORMATION FOR SEQ ID NO:87:
          (i) SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 30 amino acids
15
               (B) TYPE: amino acid
               (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
20
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:
          Ile Trp Ser Ile Phe Ser Ser Asp Ile Val Val Gly Tyr Ala Asn His
                                               10
          Ser Ser Leu Ala Ile Met Cys Pro Ile Val Ile Tyr Thr Va:
25
     (2) INFORMATION FOR SEQ ID NO:88:
          (i) SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 29 amino acids
               (B) TYPE: amino acid
               (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
30
         (ii) MOLECULE TYPE: peptide
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:
          Ile Phe Thr Ile Phe Ser Ser Asp Ile Ala Val Gly Tyr Ala Asn His
35
          Ser Ser Ala Ala Ile Met Pro Ile Val Ile Tyr Ser Val
                       20
     (2) INFORMATION FOR SEQ ID NO:89:
          (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 24 amino acids
40
                (B) TYPE: amino acid
                (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:
45
          Lys Asn Ala Ser Ala Leu Leu Ser Val Ile Ile Asn Ser Ile Gly
          Gly Asn Val Val Thr Ala Val Ser
     (2) INFORMATION FOR SEQ ID NO:90:
50
          (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 22 amino acids
                (B) TYPE: amino acid
                (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:
55
          Tyr Phe Leu Met Ser Leu Ala Val Thr Asp Leu Val Val Ser Phe Val
                                               10
```

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40

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Met Pro Val Ser Ala Leu 20

```
(2) INFORMATION FOR SEQ ID NO:91:
```

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91: 10 Ala Ile Thr Lys Ile Ala Ile Thr Trp Ala Ile Ser Gly Val Ser Val 10

Pro Phe Ile Pro Val Trp Gly

(2) INFORMATION FOR SEQ ID NO:92: 15

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 24 amino acids
 - (B) TYPE: amino acid
- (C) STRANDEDNESS: single (D) TOPOLOGY: linear 20
 - (ii) MOLECULE TYPE: peptide
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Leu Gly Ile Ile Phe Gly Thr Phe Ile Ile Ile Trp Leu Pro Phe Phe 10

- 25 Ile Thr Asn Leu Val Ser Pro Ile 20
 - (2) INFORMATION FOR SEQ ID NO:93:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23 amino acids
- 30 (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: peptide
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:
- Ile Trp Ile Ser Leu Asp Val Leu Phe Ser Thr Ala Ser Ser Ile Met 35

His Leu Cys Ala Ile Ser Leu 20

- (2) INFORMATION FOR SEQ ID NO:94:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 45 (ii) MOLECULE TYPE: peptide
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:
 - Gly Tyr Thr Ile Tyr Ser Thr Leu Val Thr Phe Tyr Ile Pro Ser Val

Ile Met Val Ile Thr Tyr Gly 50 2.0

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STRANDEDNESS

- (D) TOPOLOGY: linear
- 11. MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

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Leu Leu Asn Phe Phe Asn Trp Ile Gly Tyr Leu Asn Ser Leu Ile Asn 1 10 15

Pro Val Ile Tyr Thr Leu Phe 20

ENGLY ELLEN AND HARMAN

WHAT IS CLAIMED IS:

- 1. A G-protein coupled receptor polypeptide, consisting essentially of an amino acid sequence of 15 to 40 amino acids substantially corresponding to a fragment or consensus peptide of a transmembrane domain of a G-protein coupled receptor, wherein said polypeptide has a GPR-related biological activity selected from binding a GPR ligand or modulating GPR ligand binding to a GPR.
- A polypeptide according to claim 1, wherein said polypeptide is selected from a synthetic polypeptide, a recombinant 10 polypeptide or a purified polypeptide.
- 3. A polypeptide according to claim 1, wherein said G-protein coupled receptor is a receptor selected from a cAMP receptor, an adenosine receptor, a β -adrenergic receptor, a muscarinic acetylcholine receptor, an α -adrenergic receptor, a serotonin receptor, a histamine H2 receptor, a thrombin receptor, a kinin receptor, a follicle stimulating hormone receptor, an opsin, a rhodopsin, an odorant receptor, a cytomegalovirus receptor, or a mas oncogene GPR.
- 4. A polypeptide according to claim 1, wherein said transmembrane domain is selected from at least one of transmembrane domain TM1, TM2, TM3, TM4, TM5, TM6 or TM7.
 - 5. A polypeptide according to claim 3, wherein said transmembrane domain is a D_2 receptor transmembrane segment III or segment V.
- 25 6. A polypeptide according to claim 4, wherein said polypeptide has the amino acid sequence of Fig. 2 (SEQ ID NO:2).
 - 7. A polypeptide according to claim 4, wherein said polypeptide has the amino acid sequence of Fig. 3 (SEQ ID NO:3).
- 8. A polypeptide according to claim 4, wherein said polypeptide has an amino acid sequence selected from one of SEQ ID NOS:80-95.
 - 9. A polypeptide according to claim 4, wherein said polypeptide has an amino acid sequence of one of SEQ ID NOS:96-348.

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- 11. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:226-289.
- 12. A polypeptide according to claim 9, wherein said 5 polypeptide has an amino acid sequence from one of SEQ ID NOS:290-297.
 - 13. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:298-324.
- 14. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:325-338.
- 15. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:339-15 348.
 - 16. A polypeptide according to claim 3, wherein said transmembrane domain is a dopamine receptor transmembrane domain selected from the group consisting of a D_1 , D_2 , D_3 , D_4 or D_5 transmembrane domain.
- 17. A composition comprising a polypeptide according to claim 1, or a pharmaceutically acceptable ester, ether, sulfate, carbonate, glucuronide or salt thereof, and a pharmaceutically acceptable carrier.
- 18. A composition according to claim 16, wherein said transmembrane domain is D_2 receptor transmembrane segment III or segment V.
- 19. A composition according to claim 18, further comprising a drug selected from a phenothiazine derivative, a thioxanthine derivative, a butyrophenone derivative, a dihydroindolone, a dibenzoxazepine derivative and an atypical neuroleptic.
 - 20. A method for treating a subject suffering from a pathology related to an abnormality of a G-protein coupled receptor, comprising administering to said subject a therapeutically effective amount of composition according to claim 16.
 - 21. The method of claim 20, wherein said pathology is a psychotic disorder.

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- 22. The method of claim 21, wherein said psychotic disorder is a schizophrenia.
- 23. The method of claim 20, wherein said composition is administered to provide said polypeptide, fragment or consensus peptide thereof, in an amount ranging from about 0.01 μ g to 100 mg/kg per day.
 - 24. The method of claim 23, wherein said composition is administered to provide said polypeptide, fragment or consensus peptide thereof, in an amount ranging from about $10\mu g$ to 10 mg/kg per day.
 - 25. The method of claim 20, wherein said administering is by oral, mucosal, intravenous, intramuscular or parenteral administration.
- 26. A method for producing a polypeptide according to claim 1, wherein said polypeptide is a recombinant polypeptide obtained from a recombinant host which expresses a heterologous nucleic acid encoding said polypeptide, comprising the steps of:
 - (A) providing a host comprising a recombinant nucleic acid encoding a polypeptide according to claim 1 in expressible form;
 - (B) culturing said host under conditions such that said polypeptide is expressed in recoverable amounts; and
 - (C) recovering said polypeptide produced by said host.
 - 27. The method of claim 26, further comprising:
 - (D) purifying said polypeptide.
 - 28. The method of claim 26, wherein said host is a bacteria or a eukaryotic cell.
- 29. The method of claim 28, wherein said eukaryotic cell 30 is a mammalian cell, an insect cell or a yeast cell.
 - 30. A method for producing a polypeptide according to claim 1, comprising:
 - (A) chemically synthesizing a polypeptide according

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- 31. A method for isolating a G-protein coupled receptor, fragment or consensus sequence thereof, or a protein that binds the G-protein coupled receptor, comprising
 - (A) providing a bound support, said support being bound to a polypeptide according to claim 1, or an antibody, anti-idiotype antibody, or a fragment thereof;
 - (B) contacting a sample containing said G-protein coupled receptor or said protein that binds a G-protein coupled receptor to said bound support, such that said receptor or protein is reversibly bound to said bound support; and
 - (C) recovering said receptor or protein that is attached to the bound support by dissociating the receptor or protein under conditions that cause elution or dissociation of the receptor or protein from said bound support.
- 32. A method according to claim 31, wherein said GPR is a dopamine receptor.
- 33. An antibody, anti-idiotype antibody or a fragment of said antibody or anti-idiotype antibody, that specifically displays an epitope of a G-protein coupled receptor polypeptide, according to claim 1.
 - 34. A recombinant nucleic acid comprising a nucleotide sequence encoding a G-protein coupled receptor polypeptide according to claim 1.
 - 35. A vector comprising a nucleic acid according to claim 34.
 - 36. A host cell comprising the nucleic acid of claim 34.
- 37. A host cell according to claim 36, wherein said host cell is selected from a mammalian cell, a yeast cell, a bird cell or an insect cell.
- 38. A host cell according to claim 36, wherein, when said nucleic acid is expressed as said receptor polypeptide in said host cell, a receptor binding molecule comprising said *env* binding domain binds to said receptor polypeptide.

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- 39. A host cell according to claim 37, wherein said host cell is a mammalian cell selected from a human cell, a primate cell or a rodent cell.
- 40. A method for isolating a protein that binds a 5 G-protein coupled receptor, comprising
 - (A) providing a bound support, said support being bound to a polypeptide according to claim 1, or anti-idiotype antibody thereto;
 - (B) contacting a sample containing said protein that binds a G-protein coupled receptor to said bound support, such that said protein is reversibly bound to said bound support; and
 - (C) recovering said protein that is attached to the bound support by dissociating the receptor or protein under conditions that cause elution or dissociation of the protein from said bound support.
 - 41. A method according to claim 40, wherein said GPR is a dopamine receptor.

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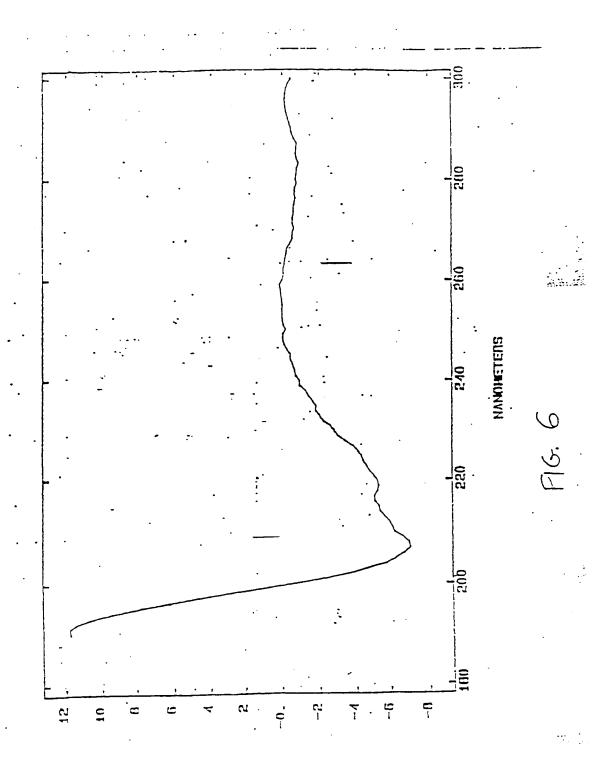
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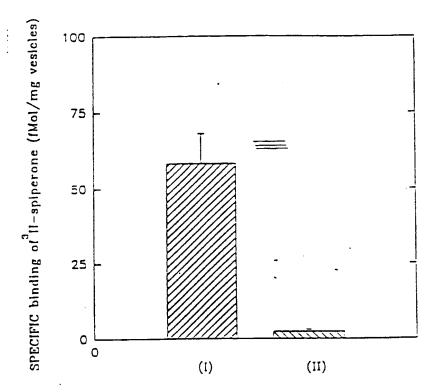
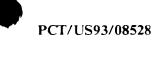


FIGURE 7



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Dog adenosine Al receptor (RDC7) (Libert et al., 1989b)
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Human beta 3 adrenerqic receptor (Emorine et al., 1989)
                   Human beta 3 adranerqic receptor (Emorine et al., 1989)
Cow alpha 1 adranerqic receptor (Schwinn et al., 1990)
Rat alpha 13 adranerqic receptor (Voigt, et al., 1990)
Human alpha 2 C4 adranerqic receptor (Regan et al., 1988)
Human alpha 2 C2 adranerqic receptor (Lomasney et al., 1990)
Human alpha 2 C10 adranerqic receptor (Kobilka et al., 1987c)
Rat alpha 2 adranerqic receptor R20 (Hanian et al., 1987c)
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                       Human dopamine D4 receptor (Van Tol et al., 1991)
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                       Numan serotonin ld receptor [RDC4] ( Ramblin and Metcalf, 1991)
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                       Human serotonin la receptor (Motika et al., 1988)
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                        Rat serotonin 2 receptor (Julius et al., 1990)
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                       Human histamine HZ receptor (Gantz et al., 1991)
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                       Numan N-formyl peptide receptor (Boulay et al., 1990)
Human CSa anaphylatoxin receptor. (Garard and Garard, 1991)
Human thrombin receptor (Vu et al., 1991)
Human thrombinane AZ receptor (Hirata et al., 1991)
Human II-4 receptor (Gurphy and Tiffany, 1991)
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                         Guinea-pig platelet-activating factor receptor (Honda et al. 1991)
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Rat non-isopeptide selective endothelin receptor (Sakurai et al., 1990)
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Rat neuromedin B preferring bombesin receptor (Wada et al., 1991)
                         Rat neuromedin B preferring bombesin receptor (Maca et al., 1991)
Numan vasoactive intestinal peptide (Sreedharan et al., 1991)
Rat neurotensin receptor (Tanaka et al., 1990)
Rat bradykinin receptor Otclachern et al., 1991)
House thyrotropin-releasing homome receptor (Straub et al., 1990)
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Kuman neurokinin A (SK) receptor (Gerard et al., 1990)

Rat substance ? receptor (Tokota et al., 1989)

Rat neuromedin K receptor (Shiqemoto et al., 1990)

Bovine adrenal angiotensin II type-1 receptor (Sasaki et al. 1991)

Human mas oncogene (angiotensin) receptor (Young et al., 1986)
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                           Numan lutropin-choriogonadotropin receptor (Frazier et al., 1990)
                           Numan thyrocropin receptor (Libert et al., 1989e)
Human follicle stimulating hormone receptor (Minegish et al., 1991)
      48.
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                            Numan rhodopsin (Nathans and Hogness, 1984)
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                             Human green opsin (Nathans et al., 1986)
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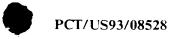
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33 34	DECEMBERATE	YAFCAVICIPINCACATIRIES-	-CIALSIVT-WATVAA-ASYTIVIH	
 35	LITELCKS SVG TVLNLEXLSV	DRYRAVASUS RVQCIGIPLV-	-DATEIVSTWILSFIL-AIPEAIGT	
36	LYPFICKASVGITVLSLCALS:	DRYRAVASASRIKGIGVPK	WEAVEIVLIWAVSVVL-AVPEAIGT	
37	TISEIGTIZACAZAŁITITITZ	DRYXAIVRPHDICASHALMX	-ICTYNTIALAZATT-YISEYAL-	
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42	CITTOTICENASSCSIEVITI	DROWNING CONTRACTOR	AVIAGINIVALAL-AFFOCEY-	
43	LOUTLING AND	DREWALIHELCPRESATATA	WIEALWIYT -YZSOCII-	
44	LCALLSTATE VELTER LYNN	DRYNGIIDPLYPRISATATX-	IVIGSTATIAFLE-AFPOCLY-	SXEXVIPOR
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FIGURE 8D



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13		LAVAGATVLCATPITTITSLIGE	CREACTYPC
14	- (77) -TISRRRARSSICTRRAVACAREKATTV	LAWIGHTVLCAFFFFFSTSLCAL	CPTOKCCVPHC
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FIGURE 8F



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A. CLASSIFICATION OF SUBJECT MATTER IPC(5) :C07K 7/00, 15/06; C12N 15/12 US CL :435/69.1; 514/12, 13, 14, 15, 16, 17; 530/387.9				
According to	o International Patent Classification (IPC) or to both r	national classification and IPC		
B. FIEL	DS SEARCHED			
Minimum de	ocumentation searched (classification system followed	by classification symbols)		
U.S. : 4	435/69.1; 514/12, 13, 14, 15, 16, 17; 530/387.9			
Documentati	ion searched other than minimum documentation to the	extent that such documents are included	in the fields searched	
APS, STN	lata base consulted during the international search (nar N/MEDLINE ms: G protein coupled, receptor#, fragment#	ne of data base and, where practicable,	search terms used)	
C. DOC	UMENTS CONSIDERED TO BE RELEVANT			
Category*	Citation of document, with indication, where app	propriate, of the relevant passages	Relevant to claim No.	
A	NATURE, Vol. 336, issued 22 Dece et.al., "Cloning and expression of a cDNA", pages 783-787. See entire do	rat D2 dopamine receptor	1-41	
A	Biochemistry, Vol. 26, No. 10, issue Dohlman et.al., "A Family of Rece Nucleotide Regulatory Proteins", page document.	ptors Coupled to Guanine	1-41	
A	BIO/TECHNOLOGY, Vol. 7, issued a et.al., "EXPRESSION OF HUMAN & RECEPTORS IN E. COLI AS A N SCREENING", pages 923-927. See es	1 AND B2 ADRENERGIC EW TOOL FOR LIGAND	1-41	
X Further documents are listed in the continuation of Box C. See patent family annex.				
· '	pocini categories of cited documents;	"T" later document published after the int date and not in conflict with the applic		
'A' do	ocument defining the general state of the art which is not considered be part of particular relevance	principle or theory underlying the im-	rention	
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Washingto	on, D.C. 2023)	Telephone No. (703) 308-0196		
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